Present Status of Insulin-Zinc Suspensions

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Much interest has been aroused of late in the new insulin-zinc modifications described in a series of reports from Hallas-Møller and associates[1, 2, 3, 4] and first reported in the American literature in 1952.[5, 6] The preparations developed in the Novo Laboratories in Copenhagen are three in number, termed semi-lente, lente, and ultra-lente depending upon relative duration of action. They have recently become commercially available in Great Britain and several European countries. Preliminary clinical trials were reported by Lawrence and Oakley,[7] and more recently by Oakley,[8] Murray and Wilson,[9] Nabarro and Stowers,[10] confirming the original clinical observations of the Danish group. The present paper presents clinical data obtained at Indianapolis in the Lilly Laboratories for Clinical Research, Indianapolis General Hospital.

Investigations of insulin preparations which have been modified in time-action to more nearly approximate the hourly needs of diabetic patients with a minimal number of daily injections have been directed, for the most part, towards combinations with insulin of agents which form insoluble compounds at the *p*H of the body. The original discovery of Hagedorn that basic substances such as the protamine, histones, globins, and kyrins combine with insulin to form insoluble precipitates resulted in a whole train of different modifications, with an almost unlimited range of onsets and durations of actions. Years of intensive clinical study of these activities has established that the most generally useful products, for the largest number of patients, are those acting in the timing range of insulin-protamine zinc insulin admixtures in the ratio of 2 to 1. That a pure crystalline compound, NPH insulin, duplicated that time action for practical purposes was undoubtedly fortuitous, and the widespread adoption of it and globin insulin attests to the soundness of the concept on which use of intermediate acting preparations was founded. All of these modifications, however, owe their efficacy to the combination of insulin with an added foreign substance of protein nature.

Even prior to Hagedorn's discovery, Scott[11] established the importance of metals of the class of zinc in the formation of insulin crystals. Zinc is a normal biological metal which appears essential to physiological function, and is actually present in the body in surprising amounts, comparable to iron. Scott and Fisher[12] directed attention to the influence of zinc in prolonging the effect of insulin and found that small quantities were ineffective whereas large quantities, e.g., 50 to 1000 mg. per 1000 units materially increased duration of action. Such high concentrations were objectionable, but this discovery was further extended practically when the Toronto observers proved that added zinc (2 mg. per 1000 units) further prolonged and intensified the action of protamine zinc insulin.

The new lente preparations depend for their efficacy upon the discovery of Hallas-Møller and colleagues that small quantities of zinc (½ to 1 mg. per 1000 units), without added foreign protein substances, result in slowly soluble complexes at blood *p*H provided certain anions, phosphate and citrate, are absent. (Phosphate is the most suitable buffer in the *p*H zone around 7 and has been habitually employed in insulin preparations that are to be adjusted to this *p*H.) The range of activity which can be produced by this method extends from that of unmodified insulin to longer than protamine zinc insulin depending upon the physical state of

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the precipitates produced (amorphous or crystalline). The so-called "excess zinc" in these preparations refers to a concentration of 0.2 mg. of zinc per 100 units of insulin. This is about 5 to 10 times the concentration utilized in preparing zinc insulin crystals USP and represents the same amount as that present in protamine zinc insulin.

TABLE 1

Zinc content of various insulin preparations

Insulin Preparation	Zinc Content Per 100 Units	Other Constituents
Amorphous Insulin	0.0 to .04 mg. (USP)	No Buffer
Zinc Insulin Crystals	.016 to .04 mg. (USP)	No Buffer
NPH Insulin	.016 to .04 mg.	1) .39 to .55 mg. protamine per 100 u. depending upon isophane point. 2) Na_2 HPO_4 Buffer
Protamine Zinc Insulin	0.20 to 0.25 mg. (USP)	1) 1.0 to 1.5 mg. protamine per 100 u. 2) Na_2 HPO_4 Buffer
Globin Insulin With Zinc	0.25 to 0.35 mg. (USP)	1) 3.6 to 4.0 mg. Globin per 100 u. 2) No Buffer
Insulin Semi-lente	0.2 to 0.25 mg.	Sodium Acetate Buffer
Insulin Lente	0.2 to 0.25 mg.	Sodium Acetate Buffer
Insulin Ultra-lente	0.2 to 0.25 mg.	Sodium Acetate Buffer

In the presence of an acetate buffer, there is a physical-chemical interaction of zinc and insulin so that higher concentrations of zinc actually become an integral part of the complex. Added zinc will apparently diffuse into the crystal lattice of insulin and will react chemically with it. These crystals, although appearing almost identical to standard zinc insulin crystals, however, are in contradistinction insoluble at the neutral point.

Two physical forms of high insulin-zinc suspension have been produced, and each has its distinctive time action. If *p*H is adjusted rapidly upward during the preparation of the material, an amorphous precipitate forms which is relatively rapidly absorbed when injected subcutaneously, and thus shows only a slight prolongation of action—approximately twelve hours. This material has been designated in the Danish and British literature as insulin semi-lente.

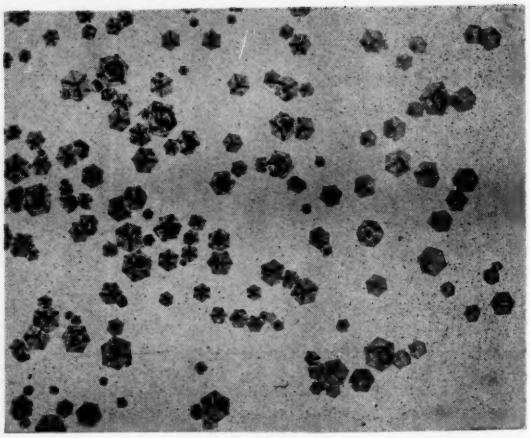

FIGURE 1

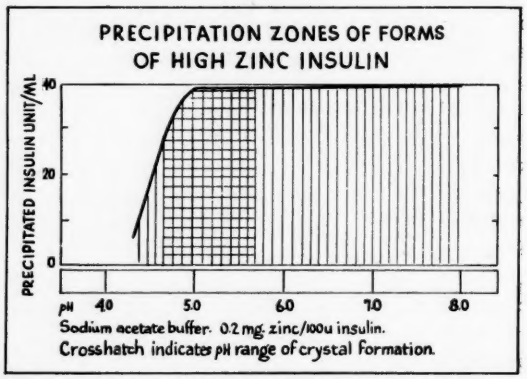

FIGURE 2

With careful adjustment of the *p*H in the range of 4.8 and 5.7, crystals of insulin-zinc form. They are extremely insoluble and display a markedly prolonged action. In one of our patients, for instance, the effect of a single large dose was exhibited over a period of 96 hours. This crystalline form has been designated insulin ultra-lente. Obviously, the time action of neither preparation is completely desirable. A mixture of the two forms consisting of 70 per cent of the ultra-lente and 30 per cent of the semi-lente has been shown by clinical studies of Hallas-Møller's group, and others to be the most efficient in meeting the average requirements of diabetic patients. This combination has been designated insulin lente.

In our studies at Indianapolis General Hospital, com-

parisons of alternating treatment periods utilizing lente insulin and NPH insulin were made since it seemed obvious that this was the time-action that would be most generally useful. The patients selected initially were those with stable or consistent behavior under hospital conditions, and alternating treatment periods were compared in the manner we have previously described.[13,14] In addition, acute experiments to determine the onset and peak of action and duration of effect were undertaken in which blood sugar levels were determined every four hours for periods of 36 hours. In these cases, equal feedings were administered every 4 hours day and night. Composites of the comparative blood sugar curves are shown in Figure 3.

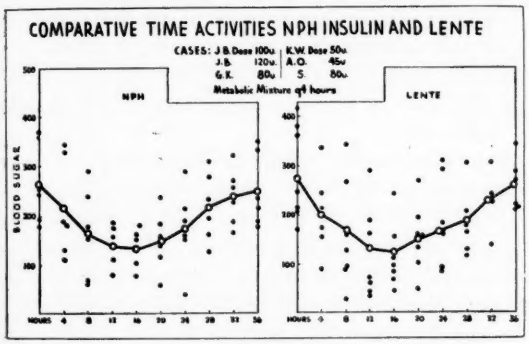

FIGURE 3

As will be seen, very little difference in either peak of activity or total duration of effect between lente insulin and NPH insulin was elicited by this technic. The curves are, for practical purposes, superimposable.

Further comparisons on a larger scale were then undertaken utilizing patients subjected to routine ward management, and again there was an apparent similarity of the responses to the two preparations. Patients of both the stable and the unstable class were selected, adjusted to hospital routine for a period of a week or more and then given the two insulin preparations alternately over four-day periods. Blood sugars were determined four times daily, and no significant differences were observed.

Since the completion of the initial studies, use of lente insulin has been further extended, and for some months it has been employed routinely on the wards of the hospital, and considerable experience has accumulated with its use in the Outpatient Diabetes Clinic. No formal comparison was attempted on the wards, the project being one of determining the utility of the preparation in ordinary management of diabetes. Transfer of cases from NPH insulin was made on a unit for unit basis. The transition has occurred smoothly, and there have been no untoward effects in a series of 47 inpatients.

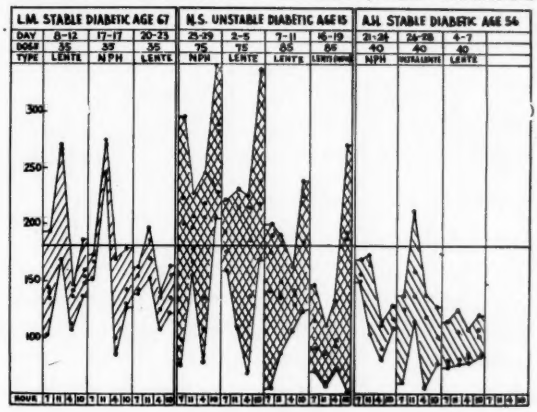

FIGURE 4

Sixty patients attending Outpatient Clinic have utilized lente insulin over periods ranging from one to five months. Our patients have become accustomed over the years to changing insulins and usually they had the impression that this was merely a different variety of NPH insulin. No essential differences in response were noted. Four patients have requested that they be returned to NPH insulin, stating that they "felt better on NPH." Laboratory and clinical findings failed to disclose any valid reason for these observations. One patient complained of pain at the site of injection, and one patient, who had been newly started on insulin a few months previously, developed insulin allergy and lipodystrophy while receiving lente insulin. This preparation was discontinued and the patient is now receiving insulin derived from a special beef source. Her complication has shown no progression.

In certain of the closely controlled patients, there was evidence that lente insulin has activity somewhat longer than NPH insulin. These individuals noted that they were again experiencing mild reactions in the evening and early morning hours. These reactions were of such mild degree that they rarely required readjustment of either diet or insulin although bedtime feedings were instituted in two instances.

Selection was made of 29 members of the outpatient group who had received lente insulin for the longest periods of time and who also had outpatient records of long periods of treatment with NPH insulin. The daily dosage of insulin varied from 10 units to 80 units, the

average for the group being slightly over 40 units. Data on these cases are briefly summarized in Table 2.

TABLE 2

Comparative results of treatment

Type of Insulin	Blood Sugar (Grand Average) Fasting	Postprandial
NPH insulin	152	237
Lente insulin	155	248

Although average differences are not significant, it was interesting to note that of the 29 cases, 16 showed lower fasting levels on lente insulin and 18 cases showed higher postprandial levels, indicating the tendency toward longer action in some patients.

DISCUSSION

These observations in the main substantiate the essential similarity in time-action and clinical efficacy of lente and NPH insulin, in that the two preparations can usually be substituted unit for unit one for the other, the chief difference being in a somewhat longer "hold-over" effect of lente, as evidenced chiefly by the occurrence of more early morning reactions in certain patients. The time-action of this preparation thus seems to conform with the established onset and duration of action that has been regarded as most efficient for general usage. The addition to the American market of three of these new preparations, including the short-acting semi-lente and very long-acting ultra-lente, from which individually tailored mixtures might be prepared extemporaneously, poses some serious problems, as this technic would be basically no different from that which was utilized intensively in clinical studies of insulin-protamine zinc insulin admixtures.

One of the serious disadvantages of the single morning injection technic of treatment has been the necessity, in severe cases, of administering supplementary doses of regular insulin, or mixing it with NPH insulin, to obtain satisfactory daytime control of the cases displaying convex twenty-four-hour blood sugar curves; or of administering a second supplementary reinforcing dose of NPH insulin later in the day in instances where the concave twenty-four-hour curve with high fasting blood sugar levels is encountered. Individual admixtures, utilizing whatever preparations the clinician chooses, have been thus far the only alternative. The question of modifying the lente preparation by addition of crystalline insulin has had some study. It may not prove to be practical on account of the effect on crystal size which is produced by alterations of *p*H. In that event, the availability of insulin semi-lente would be essential for its more rapid effect in tailor-making a preparation for the individual patient who requires a time-action different from the average case.

In any event, it appears that a noteworthy contribution has been made in that these are the only effective long-acting preparations thus far which contain no protein other than that of the insulin itself. The number of reported cases is still too small and the observations are of too short duration to justify conclusions in regard to allergic reactions. Our single case was apparently allergic to the insulin component itself. Granted that protamine-containing preparations have been in long clinical use without accumulation of positive evidence of damage, long-term toxicity is notoriously difficult to establish. On theoretical grounds, the elimination of a daily injection of such a foreign substance would not be undesirable.

Specific indications for the use of lente insulin have been suggested by Nabarro and Stowers.[10] These are (1) poor control with present insulin preparations, (2) patients requiring both morning and evening injections, (3) patients requiring protamine zinc insulin and regular insulin in the morning by separate injections, and (4) patients allergic to other types of insulin. To these might be added the cases described by Ant,[15] as representing toxicity to protamine, evidenced by unexplainable edema and signs of renal insufficiency, which symptoms are said to disappear on withdrawal of protamine insulin. Lastly, and again on purely theoretical grounds, are those cases having any evidence of tendency toward thrombotic phenomena, since protamine is a known antagonist to heparin. Evidence implicating protamine in genesis of atherosclerosis has been wanting. Nevertheless, Brown[16] has indicated that under experimental conditions accumulation of serum fat will occur following protamine administration which seems to be due to a decrease in the rate of loss of newly absorbed fat from the plasma.

SUMMARY

The steps in development of modified insulins are discussed and the discovery of the action of zinc in prolonging insulin effect in the absence of phosphate and citrate buffers is described, leading to the development of the insulin-zinc suspensions termed lente, semi-lente, and ultra-lente by the Novo investigators. Clinical experience with these preparations in the Indianapolis General Hospital since 1951 is summarized. It is con-

cluded that the lente preparation is most generally useful; its action is similar to that of NPH insulin but somewhat longer in duration.

Indications for use of these preparations are discussed, including poor control with present insulin preparations, requirement of multiple daily injections, and allergy to other types of insulin. Owing to the elimination of added protein components, the lente type of preparations represent an advance in methods available for modifying insulin.

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DISCUSSION

BLAIR HOLCOMB, M.D., (*Portland, Oregon*): I wish to express the appreciation of our group to the Eli Lilly Company, for the opportunity given us of working with insulin lente during the past year. We have been very pleased with the results.

We have had experiences with insulin lente identical with those which have been presented. We tried giving crystal insulin and lente insulin in separate injections in the morning in a few cases and found that the blood sugar was lower for the first six hours. When we gave both kinds of insulin in a mixture, the blood sugar was higher during the first six hours but at the end of eight hours, the levels were almost identical. In a few cases of "brittle" diabetes we have used a small dose of lente insulin in the evening in addition to a single dose of lente in the morning. With this procedure, I think that our stabilization is better, but we accomplished the same results when we used NPH insulin in this way.

Femoral Neuropathy in Relation to Diabetes Mellitus

Report of 17 Cases

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Neurologic lesions have been described in all parts of the nervous system in cases of diabetes mellitus but these abnormalities prove to be predominantly peripheral neuropathy or neuronopathy.[1] While almost any peripheral nerve such as the sciatic, ulnar or median may be involved in diabetic neuropathy, the femoral nerve appears to be affected most frequently in our experience, yet femoral neuropathy is scarcely mentioned in the literature. One reason for the apparent infrequency of this neuropathy may be a lack of familiarity with the condition and consequent failure to suspect its presence.

CLINICAL SYNDROME OF FEMORAL NEUROPATHY

This report deals with the syndrome of femoral neuropathy which was diagnosed in 17 cases, in 16 of which diabetes mellitus was present. There were three outstanding manifestations among these patients: pain, muscular weakness and absence of the patellar reflex. In addition to this triad, a history of paresthesia is obtained frequently.

Pain is the most frequent complaint of patients with femoral neuropathy, and was present in 15 of the 17 cases in this series. The pain may be either spontaneous or provoked by the femoral nerve stretch test (see below). Usually the pain is very severe and sharp; it may be shooting or boring in type or it may have a burning or aching quality. The pain extends from the hip along the anterior and lateral surface of the thigh into the foot, but sometimes it begins in the sacro-iliac region and radiates down the posterior surface of the thigh and leg to the dorsum of the foot. In some cases, pain may develop gradually, in others episodically. In most cases, the pain is worse at night and interferes with sleep. It may become so severe and intractable that opiates are required, and because of failing appetite, there may be loss of weight.

To confirm the diagnosis, the femoral nerve stretch test is employed. This was first called to my attention by a colleague, Dr. Sigmund Wassermann, who originally described the maneuver in nondiabetic patients.[2] The technic of the test is as follows: The patient is instructed to lie prone. By elevating the straight leg off the table, or by flexing the knee without elevation of the thigh, the femoral nerve is placed under stretch. When the test is positive, the patient complains of exquisite pain along the anterior thigh. This sign, which is actually the Lasègue sign in reverse, was positive in 9 of the 17 cases in this series. Incidentally, the Lasègue sign was negative in all of these patients, thus ruling out the possibility of sciatic neuropathy. Occasionally, it is possible to elicit pain by direct pressure on the femoral nerve, which is located laterally to the femoral artery. This sign was positive in four cases.

Muscle weakness and/or atrophy was observed in 11 cases. In the early stage of femoral neuropathy, the patient may complain of clumsiness in walking, principally in going downstairs. Later, the leg or knee may buckle and cause him to fall without warning. In order to avoid falls, some patients resort to the use of a cane. In the more advanced stages, the affected leg may become so weak that the patient is forced to remain in bed. Although the motor weakness in this condition is primarily subjective, occasionally moderate atrophy of the quadriceps muscles, the calf or even the buttocks may be demonstrable.

Absence of the patellar reflex was noted in 12 cases. In view of the intimate relationship to the function of the femoral nerve, this is not unexpected. In testing this reflex it is preferable to have the patient sit on a chair or stool, both feet planted firmly on the floor. In a normal response, contraction of the quadriceps femoris muscle is readily felt upon strik-

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ing the patellar tendon with a hammer.

In the face of the high incidence of absent achilles reflexes among diabetic patients,[1] I believe this finding has no special significance in patients with femoral neuropathy.

Paresthesia was described by 9 patients. Paresthesia is a common symptom in many peripheral neuropathies, and femoral neuropathy is no exception in this respect. The area of distribution of the paresthesia is identical with that of the pain, namely, the anterior and lateral surfaces of the thigh radiating down the leg into the foot. Numbness is a common complaint of most patients, but in some the paresthesia has a tingling quality and produces a sensation in the feet akin to that produced by electricity; in others the paresthesia has a sharp, burning character. Hyperesthesia may be a predominant complaint, and it may even be aggravated by such a slight stimulus as the contact with the bedclothes or pajamas. It is worthy of mention that the paresthesia of femoral neuropathy does not disappear as rapidly as the pain. For example, in case 16 (a physician) a feeling of coldness and tingling in the right foot persisted for five months after the severe pain had subsided, and was unaffected by the administration of vitamin B_{12}; four months after the paresthesias finally disappeared, they recurred for a brief period during a mild attack of influenza.

Elevation of the cerebrospinal fluid protein was found in three cases. The values were 97 to 158 mg. per 100 cc. In one case, the Pandy and gum mastic tests were positive. However, the spinal fluid was not examined routinely. Elevated proteins are consistent with severe peripheral neuropathy or neuronopathy.[1]

Concomitant neurologic manifestations were observed in 5 cases. The widespread nature of the neurologic disorder in diabetic patients with femoral neuropathy was shown by the involvement of other peripheral, cranial and autonomic nerves in these cases (cases 1, 4, 7, 14 and 16). Sometimes, the peripheral nerves in the shoulders and upper extremities were involved. The trigeminal and ocular were the only cranial nerves affected in this group. Autonomic nervous system disturbances were manifest in only one case (case 7); here there was diarrhea, gastric retention and absence of sweating.

Absence of the achilles reflex was noted in 8 cases. The significance of this finding in eight patients with femoral neuropathy has already been mentioned.

Objective sensory findings are infrequent in patients with femoral neuropathy. Slight hypesthesia in the distribution of the femoral nerve was noted in three cases. Position sense is usually unimpaired in this condition. Because diminished vibratory sensation is such a frequent finding in diabetic patients as a whole, its impairment in four patients with femoral neuropathy in the present series must be considered coincidental. It may be stated in passing that the diagnostic import of this finding, especially in older diabetic patients, is greatly depreciated by the high incidence in older nondiabetic individuals.[1]

Disturbances of the autonomic nervous system are not prominent in association with femoral neuropathy. A sweating test may be employed, since loss of the sweating response is an indication of degeneration of sympathetic fibres somewhere along their course in the peripheral nerves. While sweating tests were not performed routinely, in one case loss of sweating was demonstrated below the knees and in the palms of the hands. In this case, chronic diarrhea and gastric retention were further evidence of autonomic dysfunction.

RELATION TO DIABETIC STATUS

Sixteen of the 17 patients with femoral neuropathy were diabetic and only one nondiabetic. Thirteen patients had lack of control by the accepted clinical criteria, since polyuria, polyphagia, weight loss, weakness and fatigability were present. In the majority of cases, marked glycosuria was present. Hepatomegaly, another indication of poor diabetic control in our experience,[3] was found in 7 of the 17 cases. A close relationship between femoral neuropathy and poor diabetic control can be inferred from these findings.

DIFFERENTIAL DIAGNOSIS

Femoral neuropathy is a true peripheral neuropathy or neuronopathy. Herniated intervertebral disc had been suspected in several cases. The consideration of "diabetic tabes" in some cases is not surprising. Actually, there are several features of femoral neuropathy suggestive of tabes, namely, severe lancinating pain, ataxia, areflexia and, in some cases, cerebrospinal fluid changes. In my opinion, femoral neuropathy may be the underlying basis in many cases designated as diabetic "tabes" or "pseudotabes."

COURSE

With control of the diabetes by diet and insulin, the neurologic complaints of patients with femoral neuropathy usually disappeared within three months. Whereas the severe pain subsided soon after regulation of the diabetes, the residual paresthesia receded more slowly

as stated above; for example, in case 16, in which there was extremely severe pain, it practically disappeared three days after insulin administration, whereas the paresthesias, and a feeling of coldness in the foot of the affected side persisted five months longer. In every case, the pain subsided within two weeks after diabetic treatment had been instituted. Improvement of motor function usually began a few days after diabetic therapy was started, and normal muscle strength was regained rapidly, generally within three months. Recovery of the patellar tendon reflex depends upon the severity of the nerve damage. In one case, the knee jerks returned to normal within six weeks after instituting diabetic treatment. With neglect of treatment and consequent deterioration of the diabetic control, a tendency to recurrence of the neuropathy may be noted (see case 17).

TREATMENT

In my experience, the only effective treatment of diabetic neuropathies, including femoral neuropathy, is adequate management of the diabetes. A nutritious diet and a dosage of insulin adjusted to control glycosuria and hyperglycemia are essential.

In these cases, many different therapies for the relief of pain had previously been attempted elsewhere. Lumbar sympathectomy failed to alleviate the pain in two cases; in one of these a cordotomy was finally performed. Although the pain was relieved by this procedure, the patient unfortunately developed paraplegia after the operation and died from an ascending urinary tract infection. Other measures, designed to relieve pain by improving the peripheral blood flow, were uniformly unsuccessful; these included priscoline, nicotinic acid and, in one case, sodium chloride. The numerous vitamin preparations, particularly thiamin chloride and vitamin B_{12}, which have been strongly advocated by some authors, were consistently ineffectual. Of interest in this regard is case 16, in which thiamin chloride had been used daily for several years, during the time the neuropathy developed; the severe pain was alleviated promptly after treatment with insulin was begun, but paresthesias continued in spite of treatment with a 12-day course of Vitamin B_{12} in 50 μg. doses. In case 14 the administration of procaine, 2 per cent intravenously, failed to relieve the pain. Following two injections of BAL (25 mg. and 50 mg. on successive days) there was a slight diminution of the extreme hyperesthesia which, except for moderate dysesthesia in the fingers, disappeared entirely following the next two doses (100 mg.). In all other cases, after diabetic management was instituted, improvement was so prompt that no other therapy was even considered.

CASE REPORTS

Case 1. A 55-year-old male was admitted to hospital July 31, 1950, because of severe pain in the legs of several years duration, loss of weight from 190 lb. in 1945 to 118 lb., and symptoms of an acute urinary tract infection.

He had had diabetes mellitus for four years but had neglected treatment. In March 1950, very severe, boring pain developed, extending from the hips to the feet. After this, both legs became so weak that he was unable to lift them off the ground to take a step. The diagnosis was diabetic neuropathy.

He entered another hospital in May 1950. A left lumbar sympathectomy was performed without relief of pain, so that on June 19, 1950, a cordotomy was done. Although this relieved his pain, he was unable to walk again and an automatic bladder developed. The examination showed that the achilles and patellar reflexes were absent in both lower extremities. The position sense was normal. A positive Babinski sign was present on the right side and the abdominal reflexes were absent bilaterally. With the exception of elevated proteins, the cerebrospinal fluid was normal. In the opinion of the neurologic consultant, the weakness of the lower extremities and the cord bladder were sequels of the cordotomy operation. In the early stages of the neuropathy the patient had experienced paresthesias in the right hand. The course was steadily downhill and he died Oct. 16, 1950, as a result of generalized peritonitis secondary to a ruptured abscess of the prostate.

Case 2. A 54-year-old man was admitted to hospital March 17, 1951. A diabetic glucose tolerance curve had been obtained during a previous admission. The diagnosis of hemochromatosis was suspected on a second admission in September 1949. After discharge he began to notice increasing fatigue, especially during the day, nocturia (6-8 times), polyuria (every hour), and his urine was sticky. He drank a quart of milk, a large quantity of fruit juice and 6 to 8 glasses of water daily, and dropped in weight from 165 to 148 lb. in less than six months. In November 1949, he noted intermittent numbness over the lateral aspect of the right leg which occasionally had a sharp, burning character. In February 1950, his leg buckled and he fell down. On this admission both knee jerks were absent for the first time, but there were no sensory abnormalities. There were more than 100 gm. of glucose in the 24-hour urine.

During the next three months, with control of the diabetes by diet and insulin, the neurologic complaints disappeared completely. When he was readmitted in March 1951, the patellar reflexes had returned to normal.

Case 3. A 63-year-old white male was admitted to Crile (Veterans Administration) Hospital April 10, 1951. A diagnosis of diabetes was made in 1944, but he remained aglycosuric on diet alone until September 1949, when he was placed on insulin in another hospital. In October 1949, he was transferred to Crile Hospital for a transurethral resection. During three months in the hospital, the diabetes was poorly controlled. Four months after discharge, March 1950, intractable, burning pain developed in the soles of both feet, and he re-entered Crile Hospital for these complaints. Vibratory sensation was diminished in both soles, and both achilles reflexes were absent. The other tendon reflexes were present. A diagnosis of "peripheral neuritis" was made. While in the hospital, the burning pain frequently became so severe as to necessitate the administration of papaverine or demerol; the pain was not relieved by priscoline or nicotinic acid. After discharge a bilateral sympathectomy was done at another hospital without relief of pain. Postoperatively there was further weight loss leading to malnutrition, and the patient complained bitterly of pain along the anterior thighs extending into the feet. All the tendon reflexes were unobtainable and vibratory sensation was diminished in the feet and legs. The peripheral circulation was unimpaired. The diagnoses were (1) femoral neuropathy, (2) uncontrolled diabetes, and (3) malnutrition.

Case 4. A 53-year-old colored male was admitted to Crile (Veterans Administration) Hospital March 20, 1951, for the fifth time. He had been a known diabetic since 1931, and had taken insulin from 1940 until he was no longer financially able to purchase it. Soon this was followed by polydipsia, polyuria and nocturia, and he was admitted to Crile Hospital for the first time in March 1946. The right knee jerk was absent and the right ankle jerk diminished. He was discharged on a diet and insulin. He was readmitted Feb. 24, 1947, complaining of a peculiar sensation in the left side of the face and left arm "as though he were going to have a stroke." There was hypesthesia to pinprick in these areas. The fractional urines showed the diabetes to be poorly regulated. During the interval before the next admission, he did not follow his diet but apparently got along fairly well until January 1949. At this time there was stiffness of the left hip, of such severity that he had to stop work, and shooting pains and paresthesias in the right foot unrelated to exercise. There was marked weakness in the right leg which greatly interfered with walking. The right knee and ankle jerks were diminished compared with the left, which were quite lively. The diabetes was controlled by diet alone. On the next admission, Dec. 5, 1950, though moderate glycosuria was present, he had regained 12 lb. The right achilles and patellar reflexes could not be obtained. He became aglycosuric on a reduction diet. On the succeeding admission, March 6, 1951, he complained of coldness over the lateral aspect of the right thigh, right leg and foot, and over the lower half of the left leg and foot. In addition to the previously recorded absent patellar and achilles reflexes, there was impaired vibratory sensation over the entire right lower extremity, and hypesthesia to touch and pinprick over the right lower leg and foot. Position sense was normal. There was localized tenderness over the right femoral nerve and exquisite pain on stretching the femoral nerve by flexion of the knee. The diagnoses were (1) diabetes mellitus with right femoral neuropathy, (2) obesity, and (3) proximal and peripheral atherosclerosis.

Case 5. A 63-year-old white male was admitted to Crile Hospital Oct. 13, 1949. He complained of sharp, burning and tingling pain, of 10 to 12 years' duration, over the anterior and lateral surface of both thighs, radiating down the legs and producing an electricity-like sensation in the feet. The legs became so weak that he was forced to walk with a cane. A diagnosis of neuropathy had been made on a previous admission (October 1947). He had been unable to work since 1943 on account of the leg difficulty. The principal physical findings were an enlarged liver and the neurologic manifestations. The latter consisted of tenderness to pressure over the anterior surface of the thighs, especially over both femoral nerves, more marked on the right. Stretching the femoral nerves elicited pain, and there was moderate tenderness over the achilles tendon and moderate weakness of the leg muscles. There were no other objective neurologic findings. The diagnoses were (1) obesity, (2) marked dietary inadequacy with enlarged, fatty liver, (3) peripheral, mainly femoral, neuropathy, and (4) proximal atherosclerosis.

Case 6. A 55-year-old white male was admitted to Crile Hospital Jan. 9, 1951. A diagnosis of diabetes was made at another Veterans Administration Hospital in 1946. At that time he developed polyuria, polydipsia, polyphagia and loss in weight from 145-150 lb. to 112 lb. He refused to take insulin and merely curtailed the sugar-content of the diet. In November 1950, he gradually

developed pain beginning in the right sacro-iliac region and radiating down the posterior surface of the right thigh and leg to the dorsum of the foot. The pain was episodic and kept him awake at night; it was relieved by exercise and heat. After weakness of the leg appeared, he consulted a private medical clinic where glycosuria, hyperglycemia and acetonuria were found. On admission to Crile Hospital he had four-plus glycosuria, one-plus acetonuria and liver enlargement. There was wasting of the muscles of the buttocks, and he complained of pain along the posterior aspect of the right leg radiating down to the heel upon bending over. On physical examination, the Lasègue sign was negative, but with reverse extension of the thigh and flexion of the knee there was marked pain over the anterior surface of both thighs and moderate tenderness at the site of the femoral nerve in the inguinal region. Vibratory sensation was impaired in both lower extremities up to the knees. The right achilles reflex was present but the left achilles and both patellar reflexes were absent. The cerebrospinal fluid protein was 97.6 mg. Another consultant considered the possibility of a herniated disc and attributed the "neuritis" to arteriosclerosis. *Conclusion*: This patient had poorly regulated diabetes over a period of six to seven years, during which a bilateral femoral neuropathy developed. The findings cannot possibly be attributable to vascular disease in view of a normal peripheral circulation. Upon regulation of the diabetes the severe pain subsided promptly, leaving only residual paresthesias in the feet.

Case 7. A 29-year-old white male, with a history of diabetes since 1943, was admitted to Crile Hospital Oct. 25, 1950, with diarrhea. On a previous admission to Crile Hospital in 1947 for acidosis, he was discharged on a diet and insulin. In 1949 the patient had a dull, aching pain over the anterolateral aspect of both thighs. He was hospitalized at another Veterans Administration Hospital in Dec. 1949, for diarrhea. In April 1950, he complained of a burning sensation in the skin of the thighs, aggravated by contact with the bedclothes, and there was some clumsiness on walking, principally down steps. On physical examination no tendon reflexes could be elicited in the lower extremities and there was some pain on stretching the left femoral nerve. A sweating test revealed absent sweating below the knees and in the palms of the hands. The neurologic consultant reported generalized hyporeflexia. During five months of hospitalization, the diabetes was well regulated and the paresthesias, formerly present over the anterior surfaces of both thighs, disappeared. Whereas even the touch of his pajamas had been unbearable previously, now the only residual was a slight aching in the legs. Incidentally, a story was obtained of impotence, having its onset in conjunction with the diarrhea. In addition, there was marked gastric retention. When he was readmitted March 17, 1951, there was extreme dryness of the hands and feet and marked erythema of the feet which was attributed to autonomic involvement. There was generalized areflexia. *Conclusion*: Diabetic (femoral) neuropathy with neurogenic diarrhea, gastric retention and impotence.

Case 8. A 60-year-old white male was admitted to Crile (Veterans Administration) Hospital Sept. 6, 1951, with a history of onset of diabetes in 1946 (weight loss, polyuria, polydipsia and polyphagia). He was advised by a private physician to restrict the carbohydrates in the diet. In July 1951, the patient began to feel weak and easily fatigued. The glycosuria, which formerly had varied from zero to two-plus, increased to four-plus. He lost 15 lb. in weight during the next month, and this was accompanied by polyuria, polydipsia and polyphagia. On Aug. 1, 1951, the patient experienced aching pains in the legs and sharp pains in the feet. Besides, there were sharp, shooting pains along the lateral and posterior surfaces of the thighs, occurring both during the day and at night, although originally the pain had been worse at night. On physical examination, there were no significant findings with the exception of excruciating pain over the anterior thighs on stretching the femoral nerves. The diabetes was uncontrolled at the time of admission. Diagnoses: (1) Uncontrolled diabetes with bilateral femoral neuropathy, (2) proximal atherosclerosis, (3) senile emphysema, (4) fever of undetermined origin.

Case 9. A 72-year-old colored male was admitted to the Cuyahoga County Nursing Home for the second time Jan. 9, 1951. In 1931, he was admitted to a local general hospital in impending diabetic coma and, after a short period of treatment with insulin and a diet, regained his strength and returned to work. In February 1940, he began to lose weight gradually and was hospitalized because of pains in the knees. Despite an increase in insulin dosage, the pains in the legs became excruciating and a progressive weakness in the legs virtually prevented his walking. Upon admission to the Nursing Home, shortly afterwards, he had lost 35 lb. from his optimum weight and complained bitterly of severe burning pain bilaterally extending from the right sacro-iliac region along the lateral aspect of the thigh. The pain was particularly severe at night. There was a noticeable

weakness of the right leg with some atrophy (½ in. at mid-calf and mid-thigh). There was diminished sensation to pinprick beginning in the right sacro-iliac region and extending down along the leg and foot. Vibratory sensation was diminished in both lower extremities and the achilles and patellar reflexes were absent bilaterally. The provisional diagnoses were: (1) diabetes mellitus, (2) generalized arteriosclerosis, and (3) probable diabetes tabes. The cerebrospinal fluid protein was elevated to 158 mg. and there was a positive Pandy and a gum mastic of 2443210000. Prior to admission to the Nursing Home, the patient had been given large doses of thiamin chloride and sodium chloride for relief of pain. Four months after treatment of the diabetes with diet, insulin and a course of thiamin chloride, 50 mg. intravenously, he was able to move the right leg somewhat better and the pain and burning were less severe than before. He had gained weight and appeared much better.

Case 10. A 68-year-old white male, a private patient, was examined Feb. 18, 1950. In 1949 he had developed an increased appetite with a great desire to eat "sweets," polydipsia, nocturia and a moderate weight loss. He consulted a physician, who prescribed a diet in which sugar and starches were omitted. One month before consulting me, an aching pain developed over the anterior surface of his left thigh, and this was accompanied by a less severe pain over the lower spine and weakness of the left leg, which gave way occasionally. The patient was underweight and presented hepatomegaly. The left patellar reflex was absent, the right patellar and both achilles reflexes normal. There was marked tenderness and pain upon acute flexion of the knee (Wassermann's sign). Diagnoses: (1) diabetes mellitus, poorly regulated, with femoral neuropathy, (2) diabetic retinopathy, (3) proximal atherosclerosis, (4) hypertrophic arthritis, (5) underweight.

Case 11. A 61-year-old white male was examined as a private patient Nov. 7, 1952. He gave a history of polydipsia, polyuria with nocturia (times two to three), and a 10 lb. weight loss over the preceding two years. In recent months he had experienced pain and paresthesia over the anterior surface of both thighs. Five weeks previously he was hospitalized because of a rectal abscess and found to be in keto-acidosis. Although all the reflexes were obtained, pain was elicited bilaterally over the anterior thighs by means of the reverse Lasègue sign. Diagnoses: (1) diabetes mellitus with femoral neuropathy, (2) senile emphysema, and (3) peripheral atherosclerosis.

Case 12. A 48-year-old pharmacist was examined Aug. 21, 1952, complaining of a "limping" feeling over the anterior and outer surface of the left thigh. The diabetes had been discovered eight years previously in the course of a life insurance examination. He was given a diet which he did not follow. In 1949 he consulted me for the first time because of nocturia, frequency and polydipsia. Although he reduced the intake of starches voluntarily, nevertheless 15 gm. of glucose were excreted in the 24-hour urine. A moderate glycosuria persisted until the most recent examination, when 90 gm. of glucose were found in the 24-hour urine. Diagnoses: (1) diabetes, obese type, with femoral neuropathy, (2) varicose veins.

Case 13. A 71-year-old white male was referred for examination April 5, 1951. Five years previously (1946) glycosuria had been discovered during a routine physical examination and he was placed on a diet by the examining physician. While on this diet, his weight dropped from 190 lb. to his present weight of 164 lb. Two weeks previously an aching pain developed in the left leg which was much worse at night. Later, his son noted that his knee buckled frequently. Two days before consulting me, a herpetic eruption appeared over the left anterior thigh. The deep tendon reflexes were very lively but the left patellar reflex was absent. The blood sugar was 200 mg. per cent and a diabetic glucose tolerance test was obtained. The neuropathy gradually subsided during the next three months. When he was re-examined July 14, 1952, the left patellar reflex still could not be elicited. Diagnoses: (1) diabetes mellitus, borderline, with femoral neuropathy and herpes zoster, (2) proximal atherosclerosis, (3) benign prostatic hypertrophy and hydrocele, left.

Case 14. A 40-year-old white male, examined as a private patient March 28, 1951, had had diabetes for 19 years. On Aug. 15, 1950, he awakened with a feeling of numbness in the fingers and toes of the left side and paresthesias over the left side of the face. Two months later the right great toe was affected similarly. In the four-month period prior to my examination, the paresthesias in the hand and foot became unbearable and he complained also of impotence and loss of libido. The patient presented evidence of severe retinopathy, hepatomegaly and occlusive vascular disease. All the tendon reflexes were lively except for absence of both achilles reflexes. There was moderate tenderness over the femoral nerves with the reverse Lasègue sign, and considerable glycosuria was found in the 24-hour urine. The patient was hospitalized for study, and a peripheral vascular con-

sultant attributed the pain to neuropathy. This conclusion was confirmed by a neurologic consultant. The patient obtained no relief from the administration of vitamin B_{12}. Following two injections of 25 and 50 mg. of BAL, there was slight diminution of the extreme hyperesthesia, which disappeared entirely following two 100 mg. doses of BAL. Some dysesthesia in the fingers still remained. Shortly afterwards the patient expired suddenly and, because no autopsy permit could be obtained, the cause of death was undetermined. Diagnoses: (1) poorly regulated diabetes with retinopathy and neuropathy, (2) peripheral atherosclerosis.

Case 15. An 18-year-old white female, with recently discovered diabetes mellitus, was examined May 29, 1952. In the preceding two to three months, she experienced frequency of urination (8-10 times daily and 2-3 times at night), occasional urinary incontinence and severe thirst. Six weeks previously the left ankle became weak and turned readily; the leg felt numb up to the level of the knee. The principal physical findings were an enlarged liver and absence of both patellar reflexes. The Wassermann sign, that is, pain on stretching both femoral nerves, was positive. Two days after the administration of insulin, the urinary symptoms disappeared. The neurologic symptoms gradually subsided within one month, and six weeks afterwards the patellar reflexes could be obtained by re-enforcement.

Case 16. A 61-year-old white physician has been under observation since 1948. After a severe attack of mumps in 1926, the patient experienced recurrent attacks of cranial nerve paralyses (facial, oculomotor and trochlear). The diabetes was discovered through a routine urinalysis and had always been asymptomatic, although four-plus glycosuria had been present frequently after large meals. In September 1949, a diabetic glucose tolerance curve was obtained and all the deep tendon reflexes were normal, though hypoactive. Following a hard fall in March 1950, pain developed over the right lateral thigh. Shortly afterwards, he experienced paresthesias in the right foot as though he were walking on a carpet. In May 1950, a neuritic pain and hyperesthesia appeared in the left arm and the pain in the leg became so severe that the patient was unable to eat properly and lost 10-12 lb. in weight. On physical examination (June 7, 1950) he presented an enlarged liver and the deep tendon reflexes were absent in the left arm and right leg. There was no femoral or sciatic tenderness. The neurologic findings were confirmed by a neurologist who also found tenderness in the left arm on pressure. The 24-hour urine contained 36 gm. of glucose. Three days after the administration of insulin was begun, the pain had practically disappeared and the liver size receded to within normal limits. The paresthesias, and a feeling of coldness, persisted for a period of five months until November 1950. It is of interest that the patient had been taking thiamin chloride, 100 mg. daily, for many years, up to and including the time of development of the neuropathy. Also, the paresthesias were unaffected by a 12-day course of vitamin B_{12} in 50 μg. doses. In March 1951, the paresthesias recurred slightly during a mild bout of influenza. He was hospitalized for two weeks in April 1951, with a right trigeminal and ocular neuropathy characterized by severe pain in the eyeball and face persisting for six to seven weeks. There were accompanying eye muscle paralysis and diplopia, from which he recovered completely after two months. When re-examined Sept. 3, 1952, the patellar and achilles reflexes were absent bilaterally.

Case 17. A 60-year-old white male was seen in consultation Jan. 14, 1950, because of a dull, aching pain along the left anterior thigh and leg of three weeks' duration. The pain was severe, aching, worse at night, and there was weakness in the leg. A diagnosis of diabetes had been established in 1940 on the basis of polydipsia, weight loss, polyuria and polyphagia. Insulin was started in 1944. On examination, the patient presented hepatomegaly, marked glycosuria and weakness of the left leg. There was slight hypesthesia and tenderness of the left femoral nerve. Both patellar reflexes were greatly diminished; the achilles were normal. One week after the insulin dose was modified, the leg felt somewhat stronger and there was less pain; after two weeks of treatment the pain disappeared entirely. Three months later the strength in the leg had returned to normal, and two months afterwards both patellar reflexes could be obtained, two-plus on the right, one-plus on the left. In October 1950, there was a slight recurrent soreness and tenderness along the lateral portion of the left thigh, mainly at night. Diagnoses: (1) uncontrolled diabetes mellitus with bilateral femoral neuropathy and retinopathy, (2) severe proximal atherosclerosis, (3) nerve deafness.

SUMMARY

Seventeen cases of femoral neuropathy have been studied; in 16, diabetes was present. The condition is manifested by pain and tenderness in the distribution of the cutaneous branches of the femoral nerve, weakness of the muscles supplied by it and absence of the patellar tendon reflexes and paresthesia.

TABLE 1

Neurologic manifestations in 17 cases of femoral neuropathy

Symptoms and Signs	Number of Cases
Pain	15
Absent patellar reflex	12
Muscle weakness and/or atrophy	11
Paresthesia	9
Positive femoral nerve stretch test	9
Localized femoral nerve tenderness	4
Elevated cerebrospinal fluid protein (not tested routinely)	3

TABLE 2

Concomitant neurologic manifestations in 17 cases of femoral neuropathy

Findings	Number of Cases
Other peripheral nerves involved	5
Absent achilles reflex	8
Diminished vibratory sensation	4
Hypesthesia	3
Autonomic nerves affected Diarrhea, gastric retention, and absent sweating response	1
Achilles tendon hyperesthesia	1

Although the sensory symptoms are always more prominent, there is usually a motor disturbance except in mild cases. One of the early manifestations of femoral neuropathy may be a "giving way of the legs." Moderate wasting of the quadriceps muscle group may be observed but marked atrophy is rare. Absence of the patellar reflex is an important sign; the impairment of this reflex can vary from slight diminution in some patients to complete, irreversible loss.

Thorough control of the diabetes is the most important measure in treatment. It usually results in early subsidence of pain and slow but gradual recovery from the other manifestations.

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Committee to Study Artificial Sweeteners

The Food and Nutrition Board of the National Research Council, at the request of the Food and Drug Administration, has named a committee to study the principles which should govern the use of artificial sweeteners in foods for special dietary purposes.

The primary purpose of the committee will be the development of a statement of general principles and of other factors for consideration in the formulation of a policy on the use of artificial sweeteners in food.

The committee, which held its first meeting in January at Ithaca, N.Y., includes Dr. W. H. Griffith, chairman, professor of physiological chemistry, University of California Medical Center, Los Angeles; Dr. B. S. Clark, president, Institute of Food Technologists; Dr. P. L. Day, professor of biochemistry, University of Arkansas School of Medicine; Dr. Norman Jolliffe, director, bureau of nutrition, New York City Department of Health; and Dr. Charlotte Young, professor of food and nutrition, Cornell University.

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Evaluation of Screening Procedures in a Diabetes Detection Drive

A follow-up survey of individuals found to have positive urine tests

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Since 1948, when the American Diabetes Association sponsored the first National Diabetes Detection Week, the participation by local medical groups has been steadily growing. The screening technics have been based principally on the testing of urine for sugar, although in some cities this has been combined with blood glucose determinations.

Since the ultimate objective of the detection procedures is the finding of all of the presently unknown diabetics, an evaluation of the effectiveness of the screening methods employed is of primary importance.

The present study was undertaken to investigate this problem under the circumstances which prevailed during the Diabetes Detection Drive in Washington, D. C., in November 1951. Detection surveys have been conducted annually in this city and the surrounding counties since 1949. The survey method was essentially similar to that employed in most cities. Random urine specimens were collected through various channels, including drug stores, industrial and business organizations, government agencies and hospitals. There was no active participation by the municipal health agencies, except in one county, and the school systems were not included. Urinalyses for sugar were performed in several cooperating laboratories by the usually accepted methods, and the reports were finally channeled to the chairman of the drive.

To each individual found to have a positive test was sent the statement, "This does not necessarily indicate the presence of diabetes, but we would recommend that you visit your physician or a clinic for further examinations." A report of the positive test was also sent to the physician indicated on the label accompanying the specimen.

During the Diabetes Detection Week of 1951, a total of 19,828 urine specimens were tested, of which 866 (4.4 per cent) were reported positive. For the purposes of the follow-up study, a segment of 2,657 was selected, for the following reasons: (1) These specimens were collected in drug stores throughout the city, and therefore represented a random sampling. (2) The tests were all performed in one laboratory by a single trained technician, thus eliminating variations in interpretation of the results. (3) Only one testing technic, by the Galatest (R) powder,* was employed, providing a uniform testing procedure, although excluding consideration of its relative sensitivity.

Nine months after the Diabetes Detection Drive was completed, a follow-up survey of this group was undertaken, to answer the following questions:

1. What proportion of the individuals, who were notified that they had positive urine tests, subsequently presented themselves to physicians for further diagnostic studies?

2. What steps did the physicians take to establish or exclude the diagnosis of diabetes?

3. How many of the individuals with positive urine tests were ultimately proved to be newly discovered diabetics?

Presented at the Annual Meeting of the American Diabetes Association in New York City on May 31, 1953.

From the Department of Medicine, George Washington University School of Medicine, and the Veterans Administration Hospital, Washington, D. C.

This study was made possible by a grant from the Committee on Detection and Education of the American Diabetes Association.

*The authors acknowledge the aid of the Denver Chemical Company in providing the technician and the testing material.

METHOD

Of the 2,657 urine specimens included in this group 220 (8.2 per cent) were found to show positive tests, including all degrees of reduction. To each of the 220 individuals who had positive urine tests, a letter was sent inquiring if a physician had been consulted, what tests had been done, whether the tests had shown the existence of diabetes, and whether the individual had known that he was a diabetic prior to the drive.

When this form was returned, a request for similar information was sent to the physician, including also the question whether therapy had been instituted, and if so, what type. In addition, the physician was asked to allow us to perform a glucose tolerance test at no cost to the patient, the results of which would be submitted directly to the physician. If no response was received from the patient or physician, a second letter was sent, followed when necessary by telephone contact.

Prior to the performance of the glucose tolerance tests, the patients were instructed to eat an unrestricted diet for several days, and an additional meal containing 70 gm. of carbohydrate at 10 p.m. on the evening before the test. After the fasting blood specimen was drawn, 100 gm. of glucose was given orally, and venous blood samples were drawn at ½, 1, 2 and 3 hours for glucose determination by the Somogyi method. In a few instances, because of difficulty in venipuncture, capillary samples were used and analyzed by the Folin-Wu microtechnic. The chemical procedures were performed under the supervision of Dr. Joseph H. Roe, Professor of Biochemistry at the George Washington University School of Medicine.

RESULTS

Of the 220 individuals who were sent the questionnaires, 174 (79 per cent), responded (Table I). There were 97 males and 77 females. The age was given by 156 individuals, of whom 26 (17 per cent) were age 3 to 9, 22 (14 per cent) age 10 to 19, 48 (31 per cent) age 20 to 39, 38 (24 per cent) age 40 to 59, and 22 (14 per cent) age 60 to 79 (Table 2).

Of the 174 persons who answered the questionnaire, 155 (88 per cent) stated that they had reported to their private physicians or to clinics (Table 3). However, in 25 instances, as indicated below, the patients' statements were not confirmed by the physicians. If a correction is made for this discrepancy, the percentage of patients reporting to their physicians becomes 71 per cent. Sixteen of the individuals reported that they had not visited their physicians; 124 (80 per cent) indicated that no diabetes had been found, 29 (19 per cent) stated that their doctors had made a diagnosis of diabetes, and 2 (1 per cent) reported that their physicians had not performed any tests.

TABLE 1

Number of urine specimens examined in Washington, D. C. follow-up drive: 19,828

Group selected for survey		
Total number examined	2,657	
Number of positive urine tests	220	(8.2%)
Number of "urine positive" subjects submitting follow-up information	174	(79%)

TABLE 2

Sex and age distribution of 174 patients with positive screening tests who submitted follow-up information

Sex	
Males	97 (56%)
Females	77 (44%)
Age (Stated in 156 cases)	
3 to 9 years	26 (17%)
10 to 19 years	22 (14%)
20 to 39 years	48 (31%)
40 to 59 years	38 (24%)
60 to 79 years	22 (14%)

TABLE 3

Patients' reports regarding follow-up visits to private physicians

Reported to doctor	155
"Doctor found no diabetes"	124
"Doctor found diabetes"	29* (19%)
"Doctor did no tests	2
Did not report to doctor	16**

*Includes 10 previously known diabetics.
**Includes 4 previously known diabetics.

One-hundred and fifty-five questionnaires were sent to the physicians named by the patients, in response to which 130 (83 per cent) replies were received. Of these, 25 physicians indicated that they had no records of the patients having reported to them. Of the remaining 105, 49.5 per cent of the doctors had done only urinalyses, 39 per cent had also made blood sugar determinations, 8.6 per cent had performed glucose tolerance tests, and 2.9 per cent had done no tests (Table 4).

In 24 instances, the physicians stated that diabetes had been found. In this group, 14 were previously known to be diabetic, either to the doctor or the patient, and 10 were considered to be newly discovered, as can be seen from Table 4. The diagnosis in these 10 cases was based on glucose tolerance tests in 2, blood sugar and urine tests in 6, urinalysis alone in 1,

TABLE 4

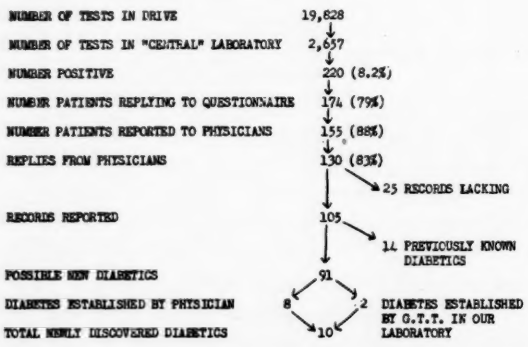
Diagnostic tests performed by physicians who returned questionnaires

	Total	Urinalysis alone	Blood sugar & urinalysis	Glucose tolerance test	No tests reported
No diagnosis of diabetes established	81	45	27*	7	2
Diagnosis of previous diabetes confirmed	14	6	8**	0	0
Diagnosis of diabetes newly established	10	1	6	2	1
Per cent of total	100%	49.5%	39.0%	8.6%	2.9%

*3 Postprandial
**1 Postprandial

and no test reported in one. For the purposes of analysis, the last 2 cases were excluded because the evidence was considered inadequate. Therefore, of the 91 patients who presented themselves to their physicians with possible diabetes which had previously been unrecognized, 8 (8.8 per cent) were found by their doctors actually to have diabetes (Figure 1).

FIGURE 1



Glucose tolerance tests were performed in our laboratory in 50 cases (Table 5). In 47, normal curves were obtained. One of these patients had been considered a diabetic by the physician on the basis of a urinalysis and fasting blood sugar, and was being treated by diet. In 12 instances, since the patients had no family physicians, no tests had been done. In one instance the urine test by the physician had been positive, but the fasting blood sugar normal. In 24 the physicians had done only a urinalysis, which was negative, and in 10 a normal blood sugar and urinalysis had been found.

TABLE 5

Results of 50 glucose tolerance tests performed by our laboratory

	Total	Previously known diabetic	Considered by physician as nondiabetic: Urinalysis alone	Considered by physician as nondiabetic: Urinalysis & blood sugar	Considered by physician as nondiabetic: Patient did not visit physician
Normal curve	47	1	24	10	12
Diabetic curve	3	1		1	1

Of the 3 patients with abnormal glucose tolerance tests, one had previously been found to be diabetic, one had not visited a physician, and one had been considered as nondiabetic on the basis of a negative urine and a fasting blood sugar of 110 mg. per 100 cc.

DISCUSSION

In the evaluation of these findings, no attempt will be made to determine their statistical validity, because of the many unknown variables which are inherent in this type of survey. However, a few conclusions may be drawn from a review of the observations which were made.

The answer to the question, what proportion of the individuals who had positive urine tests sought further advice from their physicians, depends on which source of information is employed for analysis. The replies from the patients showed 88 per cent whereas those from the physicians indicated that only 71 per cent had reported to them. If one assumes that some of the individuals who failed to respond to the questionnaires likewise had not reported to their doctors, then it would seem that more than 30 per cent had not taken any action on the notification of their positive urine tests. Similar observations have been made by Harwood,[1] and by Getting, et al.[2]

With regard to the procedures performed by the physicians, half of the doctors who submitted information were apparently content with a urinalysis alone, including one who made a diagnosis of diabetes on that basis. About 40 per cent determined blood glucose levels in addition to the urinalysis. In only 10 per cent of the instances in which diabetes was not previously known to be present was a glucose tolerance test performed. No tests were done in three cases, in one of which the physician nevertheless indicated a newly established diagnosis of diabetes.

As to how many individuals with positive urine tests and without previously known diabetes were ultimately found to be newly discovered diabetics, our information would indicate a proportion of 9.6 per cent (Table 6). This figure may be compared with that of Wilkerson and Krall,[3] from whose statistics we have calculated that approximately 8 per cent of the individuals with initial glycosuria were ultimately found to have undiagnosed diabetes. Similarly, Sharkey and his associates,[4] found 8 per cent of new diabetics among those with glycosuria.

The evaluation of the effectiveness of the "detection drive" approach to the discovery of the previously unrecognized diabetics is a most difficult one. The factors which must enter into such a consideration are: (1) The benefit derived by the individual whose diabetes is discovered early in his disease, and who is thereby brought under proper therapy at a time when it may be of considerable importance to him; (2) the total number of "new" diabetics found; (3) the relationship of this number to the total estimated undiscovered new diabetics; (4) the effort and cost involved in achieving the result; (5) the value of the educational aspects of the campaign.

There is no doubt that to the newly discovered individual diabetic the achievement may be considered 100 per cent successful. However, the results of the present analysis should also be examined from the viewpoint of the ultimate aim of the drive to uncover a maximum number of the unknown diabetics. On this basis, it would appear that this particular detection campaign failed, in that probably 99 per cent or more of the unrecognized diabetics remained undetected (Table 7). Although the actual cost involved was relatively small, the effort expended by the physicians and lay people* who conducted the drive seemed, to them at least, to be rather large. The education of the population as a whole, through the media of newspapers, radio and television, regarding the fact that diabetes is a disease which may be readily recognized and treated, appeared to be highly successful, so far as could be judged by general comment.

The factors which limited the numerical success of the drive seemed to be the mechanism of collecting and submitting urine specimens by the individuals, and the lack of interest and cooperation by the practicing physicians. A simpler procedure, such as the use of the Dreypak (a device for collecting dried urine specimens), and a more intensive campaign directed towards the physicians, may produce more significant results.

*Particular recognition is given to the unstinting cooperation of the members of the Washington Chapter, National Council of Jewish Women.

TABLE 6

Newly discovered diabetics

Total number	10*
Proportion of total (104) previously unknown diabetics in whom adequate information was obtained	9.6%
Proportion of entire sample (corrected for estimated previously known diabetics)	0.7%

*Two of these required insulin therapy, 15 and 24 units respectively.

TABLE 7

Evaluation of diabetes detection drive in Washington, D.C. November, 1951

Total number of positive tests in drive	868
Estimated ratio of patients who would act on positive report	75%
Number (868 x 75%)	651
Estimated per cent known diabetics	11%
Residual [651—(651 x 11%)]	579
Estimated total newly discovered diabetics (579 x 9.6%)	56
Total population in area covered by drive	1,600,000
Total estimated undiscovered diabetics (1,600,000 x 0.7%)	11,200
Estimated per cent "yield" (56/11,200 x 100)	0.5%

SUMMARY

1. A follow-up survey was made up of a selected segment of 2,657 urine tests performed during the Diabetes Detection Drive in Washington, D. C., in November 1951.

2. Of the 220 individuals in this group who had positive tests for sugar in the urine, 79 per cent responded to the questionnaires which were sent to them. Approximately 70 per cent of these acted upon the recommendation, which accompanied the original notification of the positive test, to visit a physician.

3. Diabetes was previously known to be present in 11 per cent. Eight patients (8.8 per cent) were found by their physicians to be previously unrecognized diabetics.

4. As part of the survey, glucose tolerance tests were performed by us on 50 individuals. In 3 of these, abnormal curves were found, one of which was in a previously known diabetic.

5. Adequate information was obtained on a total of 104 individuals who did not have previously recognized diabetes. Of these, 9.6 per cent were found to have diabetes, representing 0.8 per cent of the total number of urine tests included in the follow-up survey.

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DISCUSSION

HUGH L. C. WILKERSON, M. D., (*Boston*): This report offers valuable evidence of the need for evaluating and sharpening our tools for diabetes detection. The authors have offered good criteria for evaluating the success of a detection program, namely, the action taken by persons who have had positive screening tests and have been referred to their physicians, the action taken by their physicians and the proportion of positive screenees who ultimately were diagnosed as having diabetes.

In my opinion, the reaction of the individuals with positive tests appeared to be quite good, with 70 to 88 per cent reporting to their attending physicians. The discrepancy between the number reporting that they sought medical care and the physician's report may be due to a change in attending physician. The reported action taken by physicians when individuals were referred to them with positive urine tests were, I am sure, disappointing to all of us. The fact that in about half the cases only a recheck urinalysis was done, would in itself indicate to me that some diabetics in the group escaped detection.

This brings us to the third evaluation question: How many of the individuals with positive urine tests were ultimately considered to be diabetic? The authors estimate that among the individuals who had positive urine tests and no previous diagnosis of diabetes, about 9.6 per cent were shown to be diabetic. These findings indicate a relatively low specificity for screening by tests for sugar in the urine. The results of the 50 reported glucose tolerance tests seem to emphasize the same fact. It is worthy of note that our studies in Brookline, Mass., and elsewhere indicate that blood sugar tests are more specific as well as more sensitive for diabetes detection than urine tests.

Dr. Petrie of the Georgia State Board of Health, and Dr. McLoughlin, internist, in Atlanta, Ga., recently reported before the American College of Physicians that in the State of Georgia more than 500,000 persons since 1950 have voluntarily submitted to a screening procedure for abnormal carbohydrate metabolism. In a careful analysis of the findings in about one-half of this large number, they found that the correlation between urine and blood sugar findings on recheck of screenees who had positive blood sugar tests was inconsistent. They indicated that 20 per cent of those with grossly abnormal glucose tolerance tests had no glycosuria, that 42 per cent of those showing borderline or suspicious glucose tolerance tests had no glycosuria. In another experience with screening by urine tests in Milwaukee, the percentage of newly discovered diabetics was only 0.35 per cent of the total number tested, and in this report today the figure of 10 new diabetics found in 2657 tested, would yield a similar figure of about 0.38 per cent.

In discussing the over-all objectives of the detection program, the authors have clearly shown the inadequacy of a one-week or short-term detection effort in reaching a large proportion of the undetected diabetics in the community.

It was stated that the local health department did not play any active part in the detection program or the follow-up survey. I therefore would like to repeat my opinion that in diabetes detection, the clinician's preventive medicine approach is to the *individual* in his community—that is, to his private patient. The wide-scale public application of diabetes detection requires a public approach to the *community* of individuals and can be carried out more successfully by physicians cooperating with public health departments.

We must find ways for improving the conditions described in this report if our detection drives are to be efficient.

The Effects of Diabetic Acidosis and Coma Upon the Serum Lipoproteins and Cholesterol

Elizabeth F. Tuller, Ph.D., George V. Mann, M.D., Fredy Schertenleib, M.D., Charles B. Roehrig, M.D., Howard F. Root, M.D., Boston

The disturbances of lipid metabolism induced by diabetic acidosis have been studied repeatedly since the pioneering work of Bloor.[1] Within the limitations of the chemical methods used, most workers have agreed that diabetic acidosis is generally characterized by chemical lipemia consisting principally of neutral fat, by hypercholesterolemia, and by a variable degree of lactescence of the separated serum.[2-9]

A preoccupation with the lipid metabolism of diabetic subjects is produced by three hypotheses. First, the conspicuous predilection of diabetic subjects to atherosclerosis, as well as other forms of arteriosclerosis, may be a consequence of transitory or continuing disorders of lipid metabolism. Second, the defect in lipid metabolism in diabetes mellitus may be even more basic to the disease than is generally appreciated. Third, the extreme deviations of lipid metabolism sometimes seen in diabetic acidosis may afford a profitable opportunity to investigate the physiological mechanisms for the transport of neutral fat or other lipids. The collaborative efforts of our laboratories have been directed primarily toward the first of these considerations.

The lipids in the blood are carried in the form of lipid-protein complexes. Gofman and his associates[10] studied some of these lipoproteins by an ultracentrifugal technic and found that they could be separated into various classes or bands, designated as S_f 0-11, 12-20, etc., depending upon the density of the molecule. The measurement of the kind and quantity of these lipoprotein classes in the serum gives an indication of the state of lipid metabolism.

In the present investigation, the disturbances of these serum lipoproteins and cholesterol were studied in a group of patients who entered the hospital in diabetic acidosis or coma. The dramatic effects of treatment of diabetic acidosis upon the lipoprotein complexes of serum are described, and the proposition is considered that the premature development of atherosclerosis may be related to these lipoprotein disturbances.

These studies were initiated after observation of a 16-year-old schoolboy who was brought to the hospital in diabetic coma. Physical examination revealed lipemia retinalis, and the serum was markedly lactescent. Routine treatment with insulin and saline followed by the usual dietary measures brought about a prompt clinical recovery. Serial laboratory measurements of the serum cholesterol, lipoproteins, blood sugar, and carbon dioxide were done and are summarized in Figure 1. The tran-

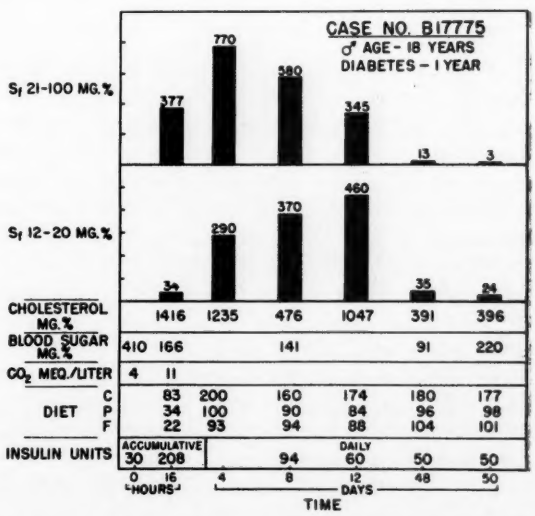

FIGURE 1. Serum lipoproteins and total cholesterol in a diabetic patient following an episode of diabetic coma.

Presented at the Annual Meeting of the American Diabetes Association in San Francisco on June 20, 1954.

From the Joslin Clinic and the Baker Clinic Research Laboratory, New England Deaconess Hospital, and the Department of Nutrition, Harvard School of Public Health, Boston, Mass.

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sient elevation of the S_f 12-20 lipoprotein band which occurred during the drop in values for the S_f 21-100 fraction, as well as the prolonged elevation above normal of both bands, excited considerable interest. A study was then planned to make similar observations in other patients.

METHODS

A total of 25 patients had two or more blood samples drawn for serial lipid determinations, although only 18 subjects were studied in sufficient detail to be considered here. Six of these were classified as being in diabetic acidosis (plasma carbon dioxide greater than 9 mEq./L.) and 12 were classified as diabetic comas (carbon dioxide less than 9 mEq./L.). The subjects studied were selected for various reasons of convenience and do not furnish a representative sample of the Clinic experience with respect either to prevalence or to any clinical characteristic of patients admitted in diabetic acidosis or coma.

The clinical care of these patients was carried out by the Joslin Clinic physicians according to their usual methods of management. The blood sugar and carbon dioxide measurements were obtained in the hospital clinical laboratory. The lipoprotein measurements were done by the methods of Gofman and others[10] and the serum total cholesterol by the methods of Abell and others.[11] Efforts were made to secure blood samples for lipid measurements on admission and at intervals thereafter during the patients' hospital stay and after discharge.

RESULTS

A clinical description and the initial laboratory findings of 18 patients admitted in diabetic acidosis or coma are given in Table 1 and Table 2. Although no precise correlation could be observed between blood sugar or carbon dioxide values and either cholesterol or lipoprotein values, a general relationship between the serum lipid deviation and the degree of acidosis was observed. In Figure 2, the initial plasma carbon dioxide is related to the S_f 21-100 and 100-400 fractions and to cholesterol. It may be seen that patients with coma showed somewhat greater elevations of serum lipid levels than did those admittted in acidosis. However, the scattering of the lipid values, particularly in the patients who were in coma, is large and probably indicates that other factors are affecting lipid metabolism.

In Figure 3 are presented the complete data obtained on four representative subjects. It is apparent from these data that the treatment of acidosis was characterized by rising CO_2 and by generally falling serum lipoprotein and cholesterol levels. However, it is also apparent that the values for cholesterol and for the various lipoprotein classes do not return toward normal at the same rate. It is also evident that in the interval of 24 to 48 hours following the initiation of oral feeding, the S_f 21-100 and 100-400 fractions show an increase in concentration. In some patients this increase has been maintained, and in others there has subsequently been a return to more normal values. It may also be noted that in certain of these young subjects treatment did not completely normalize the lipid transport system, for the S_f 0-11 band of lipoprotein and the serum cholesterol did not return to the levels expected in a person of that age and sex. These observations are discussed below in some detail.

DISCUSSION

In any discussion of the changes in concentration of components of the sera of diabetic patients under treatment for clinical acidosis or coma, it is important to consider the effect of the initial dehydration and the fluid therapy used to correct this. The patients described here received 3-5 liters of intravenous and oral fluid during the first 12-18 hours of treatment. Sufficient measurements to evaluate the state of hydration were not

TABLE 1
A clinical description of 18 subjects studied after admission in diabetic acidosis or coma

	Case No.	*Sex*	*Age (Years)*	*Years Duration of Diabetes*	*Previous Acidosis or Coma*	*Usual Insulin Required (Units)*
Acidosis	1	F	15	2	0	70
	2	M	14	11	+	40
	3	F	29	15	+	70
	4	M	32	29	0	50
	5	F	25	17	0	40
	6	M	19	10	0	100
Coma	7	F	16	5	0	62
	8	M	15	10	+	102
	9	F	15	0	0	32
	10	F	19	8	0	56
	11	F	28	4	0	40
	12	F	27	17	+	45
	13	F	44	23	0	40
	14	F	42	3	+	68
	15	M	34	1	0	56
	16	F	44	27	0	30
	17	F	26	7	+	52
	18	F	52	18	+	52

TABLE 2
The initial laboratory findings in 18 patients admitted in diabetic acidosis or coma

	Case No.	CO_2-mEq./L.	Blood Sugar Mg. per 100 cc.	Cholesterol Mg. per 100 cc.	Lipoprotein Mg. per 100 cc. S_f 0-11	S_f 12-20	S_f 21-100	S_f 100-400
Acidosis	1	15	200	276	310	120	232	24
	2	10	413	216*	120*	71	150	22
	3	12	393	233*	240*	62	95	0
	4	12	528	153*	120*	40	162	26
	5	15	934	299†	≥250*	143	129	5
	6	11	746	325*	≥300*	81	452	100
Coma	7	7	970	378‡	350‡	120	264	86
	8	3	697	327‡	≥230‡	110	390	180
	9	9	296	664	410	170	1420	≥400
	10	3	323	206	300	46	139	29
	11	8	267	330	220	88	450	160
	12	9	536	257	280	70	122	31
	13	5	556	414*	≥480*	130	368	170
	14	5	504	407*	≥450*	140	750	210
	15	4	990	399	≥300	112	361	63
	16	3	950	235	78	100	201	87
	17	3	600	364	≥300	54	70	14
	18	5	454	306	490	71	112	23

*Lipid values determined 2 hours after admission.
†Lipid values determined 4 hours after admission.
‡Lipid values determined 1 hour after admission.

The serum cholesterol and lipoprotein levels vary in normal individuals with sex and age. The S_f 0-10 class of lipoproteins constitutes the most abundant beta lipoprotein material in blood serum. The amount of this class of material correlates better with the serum total cholesterol than do the other classes of lipoprotein. The S_f 0-10 class concentration averages about 300 mg. per 100 cc. in adult human subjects and from 150 to 250 mg. per 100 cc. in children and adolescents. Little or no material of S_f 100-400 class of lipoproteins is contained in the sera of most normal subjects except for variable increases after a fatty meal. In males, S_f 12-20 values, expressed as averages of a group in each decade from 20 to 80 years of age, vary from 33 to 39 mg. per 100 cc. In females, similar values range from 24 to 39. Additional normal lipoprotein and cholesterol values are given by Keiding, Mann and their associates.[13]

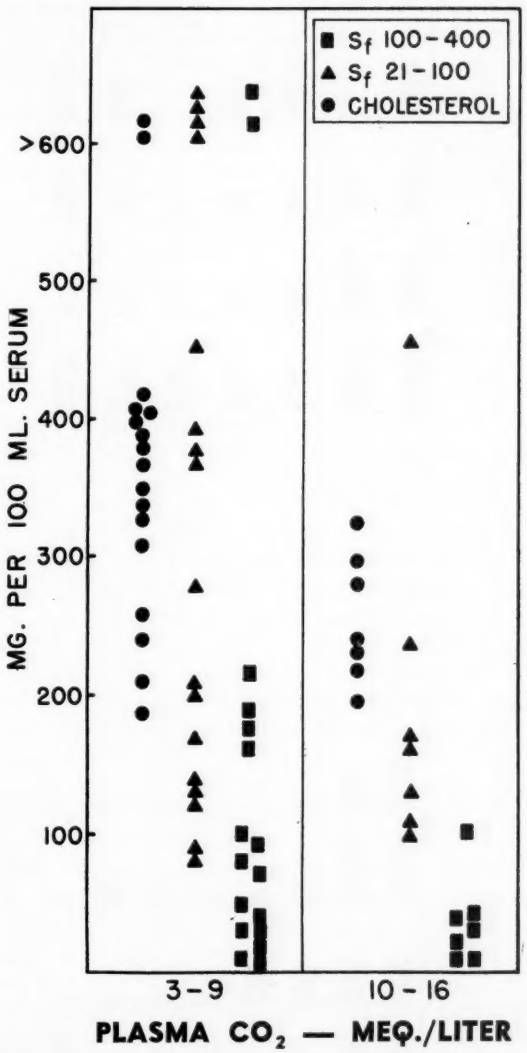
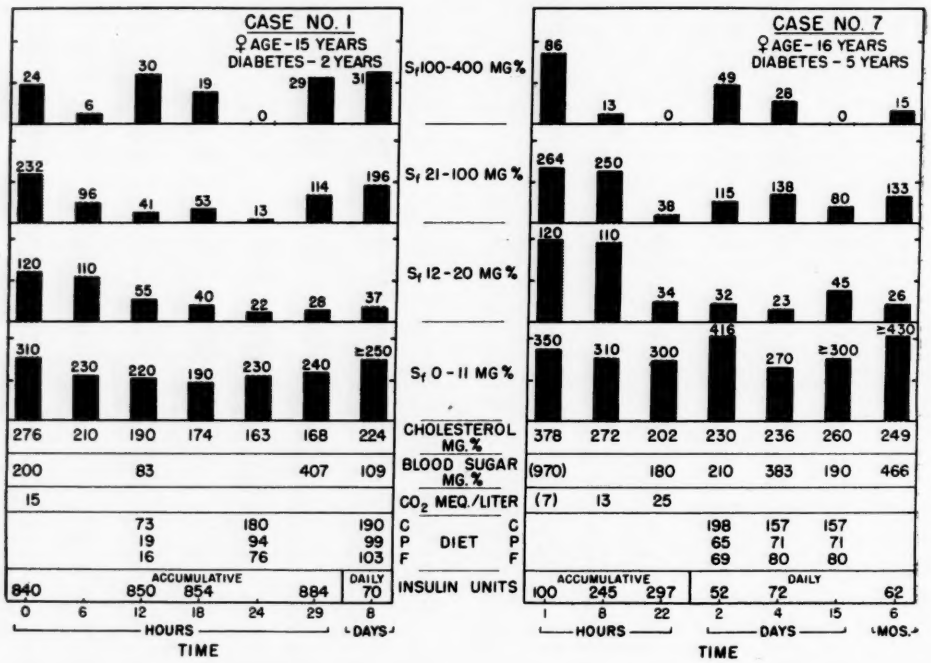


FIGURE 2. The relationship of the initial values of serum total cholesterol and serum lipoproteins to those of plasma CO_2.

done. However, regardless of the role hydration may play in the serum levels of these measured substances, the relative effect on the several lipid components should be the same. Therefore, in any comparison of the relative changes in concentration of one class of lipoprotein with respect to another or to cholesterol, the changes are real and not artefacts due to hydration of the patient during treatment. Allowing for a dilution effect on the measured serum constituents would only intensify the plateaus occasionally seen in the S_f 21-100 band and the plateaus or peaks usually seen in the S_f 12-20 band during this interval of time. With this intensification of the abnormality in level of the various fractions, the comparison of one lipoprotein band concentration with that of another would become more dramatic rather than less so.

A second question arises as to the effect of hydration of the patient on the shifts in concentration found in



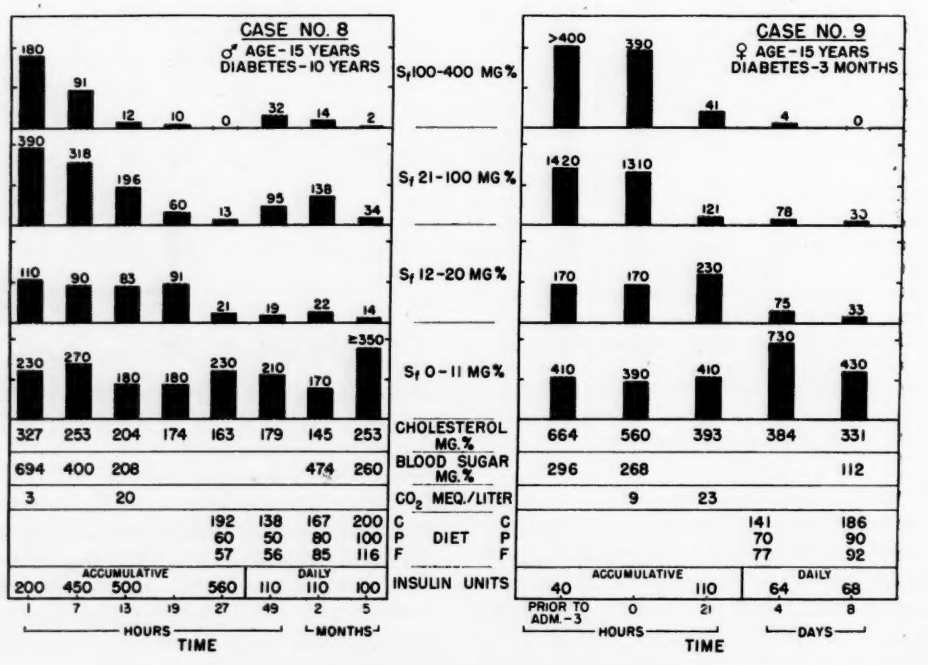


FIGURE 3. Charts of representative subjects showing lipoprotein changes during and after treatment for diabetic acidosis and coma.

any given component. Seldin and Tarail[12] have reported balance studies for patients with diabetic acidosis showing that reconstitution of plasma fluid during hydration would cause a maximum change of 55 per cent and an average change of 33 per cent in the concentration of serum constituents. Hydration would principally effect the percentage change in the first twenty-hour hours of treatment. However, taking into account the most extreme dehydration with a possible 55 per cent elevation of the measured values because of dehydration, the majority of the initial levels of the lipoproteins of the S_f 12-20, 21-100, and 100-400 classes are still higher than those of normal individuals. They are also higher than those of diabetic subjects without vascular complications or with only minimal retinopathy. As shown in the data presented by Keiding and associates[13] diabetic subjects without nephropathy would be expected to show mean levels of 44 and 52 mg. per 100 cc. in the S_f 12-20 and S_f 21-100 bands, respectively. Initial cholesterol values, after taking into account the effects of dehydration, do not show as marked elevation as do the lipoproteins.

More important than comparing a few individuals in this series with statistical summaries of other work is the illustration of the initial lipid defect in individuals by comparing initial values with those after treatment and noting the extent of the fall in concentration. Taking into account an assumed maximal concentration effect due to dehydration, 9 of the 12 patients in coma and 2 of the 6 patients in acidosis showed a drop of more than 55 per cent from the initial values of total cholesterol. In all but two of the cases not showing more than a 55 per cent drop, insulin had been given prior to admission or the first cholesterol values were determined four to six hours after admission; it might be assumed that hydration and a change in cholesterol values had already commenced. It was also observed that there was a drop in concentration from the initial values of more than 55 per cent in the S_f 100-400 lipoprotein band for all patients, in the S_f 21-100 band in all but 2, and in the S_f 12-20 in all but 5 patients. There was only one instance in the S_f 0-11 band in which such a drop in concentration was noted. It should be reemphasized that these changes are all significant despite an assumption of a 55 per cent expansion in plasma volume. If the average figure of 33 per cent is taken, all the lipoprotein classes show a real change in concentration except that of S_f 0-11. Likewise, all but two of the patients would show real changes in cholesterol levels. One of these had had insulin prior to admission, and in the other, the initial determination was made six hours after admission. It is evident from the above discussion that, whether comparisons between the concentrations of different types of lipid measurements are made or whether merely a single component is examined serially during treatment, there is a distinct and obvious lipid metabolism defect in diabetic acidosis which is quickly influenced by therapy. Although cholesterol measurements reflect the defect, the more striking evidence of it lies in the lipoprotein measurements.

A consideration of the sequence of events after treatment of diabetic coma indicated that the various lipoprotein moieties did not subside toward normal levels at equal rates. This is illustrated in Figure 3 (Nos. 1, 8, and 9). The data obtained in case 9 indicate that between the third and twenty-fourth hours of treatment the S_f 20-400 lipoprotein classes were reduced by 90 per cent. In the same interval, the S_f 0-20 classes had increased by 14 per cent. It appears futile to attempt to equate these shifts because of several technical limitations of the procedure, but an attractive explanation for the observation is the proposal of Gofman and associates[10,14] that the serum lipoproteins represent a spectrum of aggregates varying in lipid composition. These authors further proposed that the normal transport of lipid substances is accomplished by a progressive shift of material from lower to higher density, that is, from higher to lower S_f classification. This explanation would imply that in diabetic acidosis an interruption of this orderly transfer has occurred with a resultant accumulation of the low-density material in the serum. This process can be visualized as a wave phenomenon in which diabetic acidosis has acted as a dam. Treatment has broken the dam, releasing material, which has created a measurable ripple all down the lipoprotein channel.

There is some evidence that in certain of these young patients treatment did not completely normalize the lipid transport system, since the S_f 0-11 lipoprotein band and the serum cholesterol did not return to the levels expected in a person of that age and sex. This is illustrated by Figure 1 and patients No. 7 and No. 9 in Figure 3. It is also illustrated by two other patients whose initial values are listed in Table 2 (No. 5 and No. 13) and whose follow-up values after six to twelve months were 480 and 370 mg. per 100 cc., respectively, for the S_f 0-11 band and 431 and 318 mg. per 100 cc., respectively, for cholesterol concentration. In these particular individuals this persistence of abnormal levels may have been related to the presence of diabetic vascular lesions. One patient (No. 13) had diabetic retinopathy prior to this episode of diabetic coma. The other (No. 5) had retinitis proliferans prior to this admission and developed

clinically detectable nephropathy during the year following this coma. As has been pointed out in a previous paper,[13] diabetics with these vascular lesions tend to show high lipoprotein and cholesterol levels. In one case (No. 7) the failure of these lipid values to return to normal may have been due to the poor control reported for the interval of time between discharge from the hospital and the taking of the follow-up sample six months later. In the other two patients, however, the failure of these lipid levels to become normal cannot, at present, be explained.

The charts presented in Figure 3 show examples of the evidence for a return to somewhat higher serum lipid levels. In the second or third day of treatment, that is, within 24-48 hours after significant food intake was commenced, the serum lipoprotein fractions S_f 21-100 and S_f 100-400 increased again. A similar effect in lipid fractions was noted by Harris and associates.[9] An explanation was attempted on the basis that the first minimum was lower than normal for that individual, the norm being taken as the height attained in the four to seven day period following the acidosis episode. However, in our experience, this late increase was transitory in many (10) patients; for example, No. 7 and No. 8 as illustrated in Figure 3. These two patients also emphasize the influence of poor control of diabetes upon the serum lipid measurements. The first follow-up sample of patient No. 7 was taken on the fifteenth day which was obtained ten days following discharge from the hospital. During this interval she was in a diabetic camp, and her disease was under good control. The S_f 21-100 and S_f 100-400 lipoprotein concentrations had dropped from the second peak value observed in the hospital. However, in the intervening six months before the final sample was obtained, the patient admitted to being in poor control, and the concentration of these lipoprotein classes had again risen. In the other patient (No. 8), the two months' follow-up sample was obtained between two other admissions to the hospital in acidosis and coma. The S_f 21-100 and S_f 100-400 concentrations remained elevated. However, in the two months prior to obtaining the final follow-up sample, the patient was, for the first time in a year, in fair control of his diabetes. It should be noted that the concentration of these two classes of lipoprotein was much lower than the transitory peak values and approximated the lowest point reached during the episode of coma and its subsequent treatment.

It was observed that in six cases, the secondary increase in concentration appeared to persist, for example, No. 1; in one or two it was never evidenced (No. 9). These two groups of patients may not exhibit real differences from the major trend of a transitory elevation of lipid concentrations, but may merely indicate that sufficient samples at the appropriate time intervals were not obtained.

Several explanations are at hand for this secondary increase in lipid levels, but none can be substantiated at the present time. It is a well-known fact in clinical circles that the coma patient may show a relapse on the second day, and the rise in lipoproteins could be a consequence of a relative reversion toward acidosis. Perhaps the net insulin deficit has enlarged as insulin doses are reduced and food intake is begun, and lipid values have increased as a result. Or perhaps the secondary lipid rise reflects a kind of lipid tolerance test following the first substantial dietary fat intake after treatment. While these hypotheses may not exhaust the possible explanations, each of them could readily be examined experimentally. However, the present studies do not permit an explanation of the cause of the secondary rise in lipoproteins during treatment of diabetic acidosis and coma.

While the degree of lipid disturbance associated with diabetic acidosis is variable among individuals, we have seen no patient in diabetic acidosis without some increase of serum lipoprotein. Whatever the potential atherogenecity of particular bands or combinations of bands of lipoproteins, the abnormality in diabetic acidosis is both so diffuse and so regular in appearance that this appears to be a reasonable contributing factor in the premature atherosclerosis characteristic of diabetic patients. This is even more important in the light of the studies showing increased lipoprotein levels in diabetic patients with vascular changes.[13, 15] It follows then, that every effort should be made to prevent acidosis as a means of preventing atherosclerosis. In addition, there is every indication from the data herein reported and from those reported by Keiding and others[13] and Barach and Lowy[15] that even generally poor control, which has not reached the stage of actual acidosis, also causes the appearance of abnormalities in the various lipoprotein bands. Thus, it could be inferred that the better the control, the less contribution lipoprotein abnormalities can make to atherosclerosis.

The extent of lipoprotein changes and the rate at which they occur during the treatment of diabetic acidosis is approached in only one other situation; namely, the administration of parenteral heparin.

Thus, diabetic acidosis offers a unique opportunity for the study of the mechanisms that influence lipid metabolism.

SUMMARY

1. Changes in lipid levels were followed during the treatment of diabetic acidosis or coma in 18 patients. Six of these patients were admitted in acidosis and 12 in diabetic coma.

2. Measurements were made of serum total cholesterol and of serum lipoproteins of the S_f 0-11, 12-20, 20-100, and 100-400 classes as well as the routine determinations of blood sugar and carbon dioxide.

3. Diabetic coma is associated with a greater lipid disturbance than diabetic acidosis as indicated by the levels of total cholesterol, S_f 21-100 fraction, and S_f 100-400 fraction of lipoproteins. There is, however, such variability in this relationship that it appears that the basic lipid disturbance is complex and cannot be explained as a simple consequence of the degree of ketosis.

4. Treatment leads to a correction of the lipid substances toward normal levels. There is evidence of a sequential transfer of material through the spectrum of lipoproteins.

5. In the 24- to 48-hour interval following return to substantial food intake the lipoprotein concentrations often increase transitorily.

6. The abnormality of the lipoproteins in diabetic acidosis and the apparent relationship of the degree of control of the diabetes to the premature development of atherosclerosis in diabetic subjects is discussed.

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DISCUSSION

H. C. SHEPARDSON, M. D., (*San Francisco*): Dr. Howard F. Root and his co-workers in the Joslin Clinic have undertaken investigations of the details of lipid metabolism in diabetic subjects. This discussion of the effects of diabetic acidosis and coma upon the serum lipoproteins is a report of one step in this study which began several years ago.

The work of Gofman focused the attention of investigators on the possible importance of various lipoproteins in the development of atherosclerosis. The predilection of diabetic subjects for this complication has been noted for many years. Various morbific factors have been suggested in the past, none of which, however, have satisfactorily explained the premature development of vascular sclerosis in diabetics. It is possible, of course, that the disturbance in metabolism of the large molecular lipoproteins may eventually prove to be the primary inciting disturbance eventuating in the development of clinical atherosclerosis. Certainly there can be no better group of individuals on which study of the lipoprotein metabolism can be carried out than diabetics.

Technical analysis of the results obtained in this experimental work has been satisfactorily accomplished by Dr. Root. In general, however, the results suggest that the severity of diabetes, as measured by the insulin dosage, is far less important as a cause of disturbed lipid metabolism than is the degree of control of the diabetes. Thus, some two years ago Dr. Root reported a higher mean level of serum lipids in diabetic subjects who previously had been poorly controlled, as compared to those subjects who had maintained good control. This present work was carried out on some 18 patients who were either in acidosis or coma—certainly an indication of poor control. Proper treatment of the acidosis lead to a correction of the abnormal level of lipid substances toward normal.

This work would appear, therefore, to suggest strongly that the efforts of the clinician should be directed not only to the prevention of acidosis as a means of preventing atherosclerosis, but also to the maintenance of continuous and rigid control of the disease. Only in such fashion can abnormalities in the various lipoprotein bands be reduced to a minimum—a condition that apparently is essential if the atherogenicity of the lipoproteins is ultimately established. If a continuous state of perfect control is maintained it seems likely that the predilection of diabetic subjects to atherosclerosis will be reduced or even prevented.

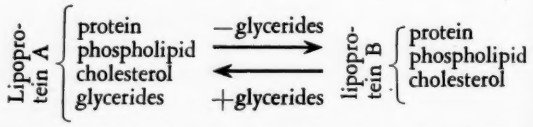
FELIX O. KOLB, M.D., (*San Francisco*): Were there any signs of xanthomatosis in any of your cases?

HOWARD F. ROOT, M.D., (*Boston*): Thank you for that question. None of the patients in this series happened to have xanthoma, but the first patient was a young man of eighteen years who had lipemia retinalis.

Some Aspects of the Chemistry and Biochemistry of Cholesterol

Cholesterol, discovered by Chevreul in 1815 and readily available for experimentation from gallstones or brain, has been the subject of innumerable researches for more than a century, but it still presents certain problems of interest that are under active inquiry. This solid alcohol of the formula $C_{27}H_{45}OH$ is no minor constituent of the animal body. The total quantity of cholesterol in a man weighing 65 kg. is approximately 210 gm., or 0.3 per cent of the wet weight. The largest amounts are present in the skin (51 gm.) and nervous tissue (35 gm.); the tissue concentration varies from 0.14 per cent (muscle) to 4.5 per cent (adrenal gland). The sterol normally present in plasma to the extent of 0.2 per cent is partly free (27 per cent) and partly as esters of higher fatty acids, while that present in red blood cells (0.12 per cent) and in nervous tissue (1.9 per cent) is completely unesterified. The cholesterol of herbivorous animals is derived exclusively by biosynthesis, while that of man is supplied by a combination of biosynthesis and diet. R. P. Cook has demonstrated that the intake of 0.58 gm. of cholesterol per day from an average normal diet can be increased to 6.9 gm. by a regime of menus involving consumption of 20 eggs per day.

What is the role of cholesterol? In what way or ways is it useful to the animal organism? The free cholesterol of nervous tissue appears to serve the function of forming a component of a structural unit of the tissue; Finnean has postulated a specific orientation of the molecules of cholesterol and phospholipid in a complex that, in combination with protein, constitutes the structure of myelin. It seems to me likely that the cholesterol in plasma plays a key role in the transport of neutral fat, by the mechanism suggested in the following idealized representation:



The protein may be the cart, and the lipid part of the sterol may supply a lining for reception of the cargo of other liquid. A possible function of the free cholesterol present in high concentration in the membrane of the red blood cell is to form complexes with, and so detoxify, substances that otherwise would have a hemolytic action. The metabolism of cholesterol is surely associated with that of the steroid sex hormones and cortical hormones, since Block has demonstrated conversion of cholesterol into pregnanediol, a metabolite or progesterone. It is possible that cholesterol serves as precursor both of these hormones and of vitamin D_3.

Is cholesterol, on occasion, also involved in pathological changes? It is assuredly involved in the formation of gallstones, since these are composed of free cholesterol to the extent of 70 to 80 per cent, and in hypercholesteremia, which may be attended with a three- or four-fold increase in blood level. It is involved also in arteriosclerosis, since the sterol content of arteriosclerotic aorta is 5 to 50 times that of normal aorta, but the question of whether or not cholesterol is a causative agent is still uncertain. Myxedema, a disease due to hypofunction of the thyroid gland, is characterized by lowered rate of basal metabolism and augmentation in blood cholesterol. There are some suggestions of an involvement of a spleen sterol in thrombocytopenic purpura but the evidence is very tenuous. There is also the possible carcinogenicity of cholesterol, or of some related or derived substance.

From "Some Aspects of the Chemistry and Biochemistry of Cholesterol," by Louis F. Fieser, in *Science*, May 21, 1954.

Response of Diabetic Coma to Various Insulin Dosages

Kendrick Smith, M.D., and Helen Eastman Martin, M.D.,† Los Angeles*

Over the years the treatment of diabetic acidosis and coma has presented a vexing problem to the physician and has often meant an unfortunate outcome for the patient. Although coma is admittedly an unnecessary and preventable complication of diabetes mellitus, its frequency remains high; at the Los Angeles County Hospital it accounts for approximately 5 per cent of the admissions to the Diabetic Service.

While the reports in the literature are in general agreement on the main principles of treatment, namely, the administration of adequate amounts of insulin and adequate hydration in conjunction with other supportive measures that may be required by the individual patient, there is still considerable disagreement as to what constitutes adequacy, and also as to the rate at which insulin and fluid should be given. Insulin dosages in the first twenty-four hours have varied from as little as 60 units, as reported by Crampton, Mellinger and Palmer,[1] to as much as several thousand units, as noted by Harwood.[2] The dosage schedule also varies widely, ranging from 20 to 50 units given hypodermically every 30 minutes to an amount equivalent to one-half of the blood sugar level or more.

The mortality from diabetic coma likewise has a wide range. McCullagh[3] has stated that a 10 per cent mortality of cases in actual coma is probably attained by few and that rates as high as 25 to 40 per cent still exist. Harwood[2] in 1951 reported that the mortality figures in various parts of the country varied from 2.4 to 43.7 per cent.

METHODS

It was our belief that the Diabetic Service of the University of Southern California Medical School at the Los Angeles County Hospital presented a sufficient variety and number of diabetic coma patients susceptible to sufficient control to permit comparison of the therapeutic effect of differing insulin dosages. The resident staff of this service consists of one resident physician who serves for three months and three interns who serve for one month. Every three days each intern admits and cares for patients for a 24-hour period.

During the period of this study, from May 6, 1952, to May 16, 1953, each intern on the Diabetic Service was assigned one of three specific insulin schedules for all of his patients with diabetic coma. The first schedule consisted of 80 units, the second of 160 units, and the third of 240 units. All insulin was administered intravenously at approximately two-hour intervals until the blood sugar was 300 mg. per 100 cc. or less.

Table 1 shows the method used for reducing the insulin dosage in accordance with changes in the blood-sugar level during the course of treatment. Such a procedure was believed necessary in order to prevent sudden and severe hypoglycemia in patients particularly sensitive to insulin. The interval between injections was kept as close to 2 hours as possible, but the difficulty of caring for acutely ill patients on a hospital ward service resulted in some variation in individual cases. The average minimum time between insulin doses in the 80-unit group was 100 minutes, in the 160-unit group 108 minutes, and in the 240-unit group 103 minutes. The average maximum time between doses in the 80-unit group was 160 minutes, in the 160-unit group 171 minutes, and in the 240-unit group 155 minutes.

TABLE 1
Insulin schedule: initial and subsequent 2-hour doses*

Reduction in Blood-Sugar Level	Urine Test (2-hr. Intervals)	Initial Dose 80 units	160 units	240 units
		Subsequent Dose		
Less than 20%	4+	80	160	240
20–30%	–	40	80	120
30–50%	3+	20	40	80
50–75%	2+	10	20	40
75–100%	1+	0	10	20

*Glucose is to be added when the blood-sugar level falls to 250 mg. per 100 cc. or less.

Presented at the Annual Meeting of the American Diabetes Association in San Francisco on June 20, 1954.

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†Associate Professor of Medicine, University of Southern California Medical School, and Senior Attending Physician, Los Angeles County Hospital.

The first 4 liters of fluid during the first 48 weeks consisted of 1000 cc. of 0.9 per cent saline solution, 1000 cc. of 1/6-molar sodium lactate, 1000 cc. of 0.9 per cent saline, and 1000 cc. of 1/6-molar sodium lactate, given in this order. During the last five weeks it consisted of 2000 cc. of 1/6-molar sodium lactate followed by 2000 cc. of 0.9 per cent saline. No glucose-containing fluids were administered until the blood-sugar level was 300 mg. per 100 cc. or less.

Therapy other than the above consisted of plasma, whole blood, and vasopressor drugs, usually norepinephrine, vasoxyl, or neosynephrine or all three, when the degree of hypotension warranted. Our definition of hypotensive shock was a systolic blood pressure of 90 mm. of mercury or less, or a diastolic blood pressure of 60 mm. of mercury or less.

The serum bicarbonate levels were determined by the Van Slyke titration method.[4] Blood sugar determinations were done by a modification of the Benedict method.

CASE MATERIAL

While the term "diabetic coma" has been used over the years to describe the condition of diabetic patients with varying degrees of impairment of consciousness and varying degrees of acidosis, we selected for our study only those in whom the serum bicarbonate level was 9.1 mEq/L. or less, not associated with other disease which could account for a depression of the bicarbonate level of this magnitude.

Insulin Dose, Age, and Sex (*Table 2*):

Forty-three patients with diabetic coma of this type were admitted during the fifty-three week period of the study. Twelve were treated on the 80-unit schedule, 18 on the 160-unit, and 13 on the 240-unit. The average ages for the three groups were 34.6, 48.7, and 45.3 years, respectively. The age ranges were similar for all three groups. As is true of our diabetic hospital patients as a whole, females predominated.

Admission Blood-Sugar, Serum Bicarbonate, Serum Potassium, and NPN Levels (*Table 3*):

The blood-sugar levels at the time of admission for all three groups were between 380 and 1230 mg. per 100 cc., with both extremes in the 80-unit group. The average levels were 688, 755, and 820 mg. respectively for the 80, 160 and 240 unit groups.

The range of bicarbonate levels on admission was restricted by design and was 3 to 10 mEq/L., as shown in Table 3, only two cases having a level higher than 9.1 mEq/L. The averages for the three groups were 6.4, 5.4, and 7.0 mEq/L.

TABLE 2

Number and age of patients by dosage schedule groups

	80-Unit Schedule	160-Unit Schedule	240-Unit Schedule
Number of patients	12	18	13
Age range (years)	16-70	17-83	21-76
Average (mean) age (years)	34.6	48.7	45.3
Per cent female	100.0	84.0	69.0

TABLE 3

Electrolyte and NPN levels on admission

	80-Unit Schedule		160-Unit Schedule		240-Unit Schedule	
	Range	Mean	Range	Mean	Range	Mean
	mg./100 cc.		mg./100 cc.		mg./100 cc.	
Blood Sugar	380-1230	688	440-1150	755	470-1120	820
	mEq/L.		mEq/L.		mEq/L.	
Serum bicarbonate	3-9	6.4	4-10	5.4	4.9-9.5	7
Serum potassium	3.8-7.9	5.4	3.9-5.2	4.5	3.3-7.4	4.7
	mg./100 cc.		mg./100 cc.		mg./100 cc.	
Nonprotein nitrogen	25-103	53	34-114	70	47-112	76

Seventeen of the 43 patients had serum potassium determinations at the time of hospital entry. These ranged from 3.3 to 7.9 mEq/L. with averages of 5.4, 4.5, and 4.7 mEq/L. Electrocardiograms were made on admission in many of the other cases; we believe this is usually a rapid and rather accurate means for the diagnosis of hypopotassemia and hyperpotassemia.

The values for nonprotein nitrogen of the blood on admission averaged well above the upper limits of normal, being 53 mg., 70 mg., and 76 mg. per 100 cc. for the 80-unit, 160-unit and 240-unit groups, respectively. All the admission levels were above normal in the 240-unit group (from 47 to 112 mg.). In the 80-unit group they ranged from 25 to 103 mg. and in the 160-unit group from 39 to 114 mg.

THERAPY

Fluid and Electrolytes (*Table 4*):

The rate of flow of intravenous fluid was ordinarily as fast as the solutions would run by gravity. It averaged 630, 780, and 560 cc. per hour for the entire period of coma for the 80-, 160-, and 240-unit groups, but approached 1000 cc. per hour during the first two to three hours. The total volume averaged 4880 cc. for the 80-unit group, 6535 cc. for the 160-unit group, and 4460 cc. for the 240-unit group.

TABLE 4
Fluid and electrolytes during coma treatment

	80-Unit Schedule		160-Unit Schedule		240-Unit Schedule	
	Range	Mean	Range	Mean	Range	Mean
	vols./cc.		vols./cc.		vols./cc.	
Fluid	1900-7800	4800	2550-8500	6535	2350-7000	4460
	gm.		gm.		gm.	
Sodium (i.v.)	5.7-21.5	15.9	7.4-27.7	16.9	8.4-24.7	15.4
Potassium						
i.v.	0-7.0	3.8	0-5.5	2.8	0-4.8	2.2
Oral	0-6.0	2.4	0-3.5	2.6	0-7.0	—*

*3 cases only.

The amount of sodium administered in the above fluids averaged 15.9 gm. or 692 mEq. for the 80-unit group, 16.9 gm., or 735 mEq. for the 160-unit group, and 15.4 gm., or 670 mEq. for the 240-unit group.

The end point in measuring the fluid volumes and sodium quantities was the same as for insulin, namely, the termination of clinical evidence of coma or the fall in the blood-sugar level to 300 mg. per 100 cc., whichever was earlier.

The data on potassium therapy are disappointing. Despite our long-held beliefs, written directions, and repeated conferences with the attending and resident staff personnel, there remains an obvious reluctance on the part of interns to administer potassium salts parenterally in amounts that we believe advisable in the treatment of diabetic coma. Part of our coma regimen calls for 1.0 gm. of potassium chloride in each liter of intravenous fluid as a minimum, if urinary output is satisfactory, and 2.0 gm. orally or by stomach tube every four hours for the first twenty-four hours.

Six of the 43 patients in the series received no potassium parenterally; one of them died. Three patients received less than 0.75 gm. The average amount given was 3.8 gm. for the 80-unit group, 2.8 gm. for 160-unit groups and 2.2 gm. for the 240-unit group. While 5 patients survived without benefit of potassium therapy, a study of the deaths in this series clearly indicates that potassium is a part of the therapy of coma that cannot be left to chance with impunity.

Insulin Therapy:

As would be expected with these schedules, more insulin on the average was administered in the 240-unit group than in the other two groups to end the coma. In determining the effectiveness of insulin therapy we believe that the essential points to be considered are: (1) the time required for clinical recovery from coma, (2) the time required to lower the blood-sugar level to 300 mg. per 100 cc. or less, and (3) the time required to elevate the bicarbonate level to 20 mEq/L. or more (Table 5). When the end point of the coma was taken to be the clinical appearance of the patient, a blood-sugar level of 300 mg. or less, or death, whichever came first, the insulin dosage for the 80-unit group averaged 271 units for the living cases and 393 units for all cases, the 160-unit group averaged 405 units for the living cases and 530 units for all cases, and the 240-unit group averaged 805 units for the living cases and 836 units for all cases. (See Figure 1.)

TABLE 5
Time required for recovery from clinical and chemical coma

	80-Unit Schedule		160-Unit Schedule		240-Unit Schedule	
	Range	Mean	Range	Mean	Range	Mean
Hours to end of clinical coma	4.5-18	9.2	2.5-17	8.8	4-12	7.4
Hours before blood sugar 300 mg./100 cc. or less	4-12	5.9	3.5-16	5.9	4-21.5	6.1
Hours before serum bicarbonate 20 millequiv. per liter or more	4-12	8.0	5.8-16	8.0	4-13.5	5.2

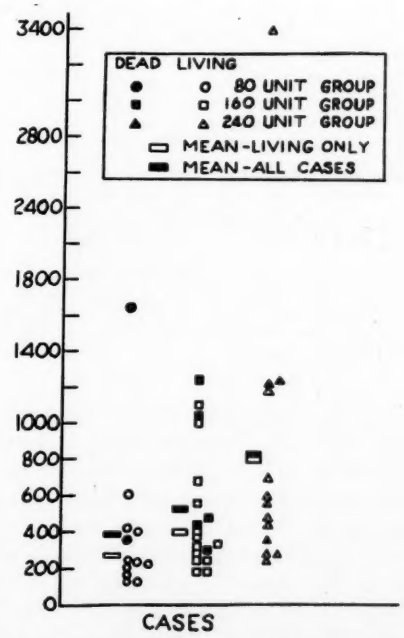

FIGURE 1. Total units of insulin received by each patient from admission to end of clinical coma, a blood-sugar level of 300 mg. per 100 cc., or less, or death, whichever came first.

Figure 2 is a graphic comparison on an arithmetic and geometric scale of the time required to end clinical coma and to reach a blood-sugar level of 300 mg. or less in the 160-unit group. The abscissa for the arithmetic scale is minutes and for the geometric scale is log of minutes, and the ordinate for both is the probability or normal equivalent deviate scale. The measurements for each case are plotted in their order of magnitude. The curved and straight lines are those derived by calculation. It is seen that the cases have nonlinear distribution on the arithmetic scale and a linear distribution on the geometric scale, with the observed points departing in random fashion from a straight line. The subsequent graphs are based on this geometric relation, in which a geometric change in effect (time) is produced by an arithmetic change in cause (dosage).

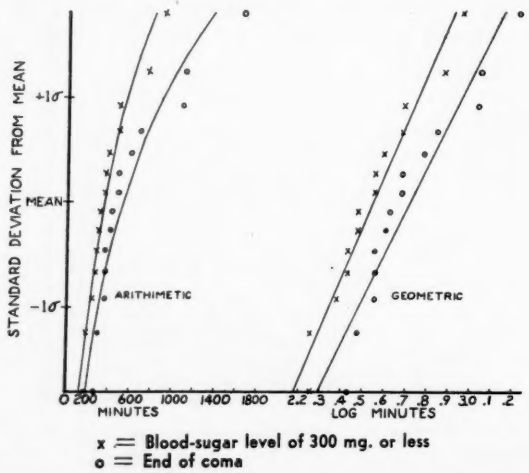

FIGURE 2. A comparison of graph types developed on an arithmetic and geometric scale of the time required to end clinical coma and to reach a blood-sugar level of 300 mg. per 100 cc., or less in the 160-unit group.

The similarity among each of the other groups in each of the three time intervals studied is shown in Table 5, in which the average time from the onset of treatment to the clinical end of coma was 9.2 hours in the 80-unit group, 8.8 hours in the 160-unit group, and 7.4 hours in the 240-unit group. While superficial inspection of these means suggests that larger dosages progressively shorten the duration of coma, the differences between pairs of these means carry probability values of 0.4 to 0.8 and are clearly not significant, and the 0.98 confidence limits of the population mean of the 34 cases combined as one group are 6.7 and 10.7 hours. Figure 3 is a graphic demonstration that the 34 patients who recovered from clinical coma in the three groups may be considered as one group normally distributed in a population of cases of diabetic coma. From the random distribution of the cases along the line, irrespective of insulin dosage, it is apparent that the duration of coma was not affected by different insulin dosages in the ranges studied.

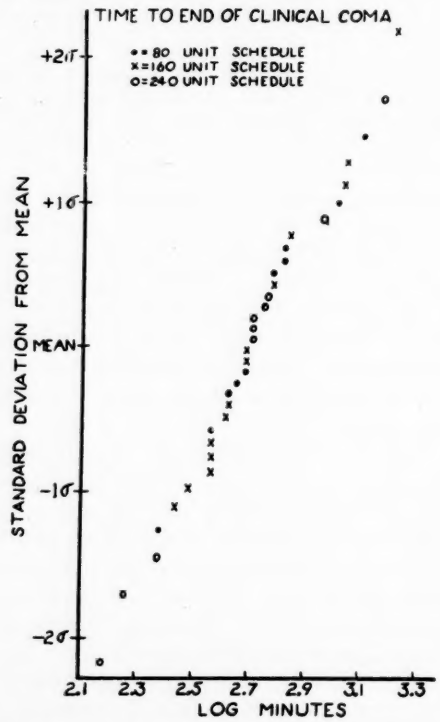

FIGURE 3. Distribution of cases in all three groups as to time to end of clinical coma.

The time required to reach a blood-sugar level of 300 mg. or less averaged 5.9 hours for the 80- and 160-unit groups and 6.1 hours for the 240-unit group. The differences between these means carry probabilities of 0.9 or more that they could have been due to chance rather than to differences in the amounts of insulin used. For the entire group of 34 cases in which the blood sugar reached 300 mg., the 0.98 confidence limits of the population mean are 4.8 and 7.3 hours. Figure 4 is a graphic presentation of the homogeneity of the cases when treated as one group.

Several limitations, however, are present in these statistics. One is that eight patients received some glucose intravenously or oral feedings before the blood-sugar level reached 300 mg., which should prolong the

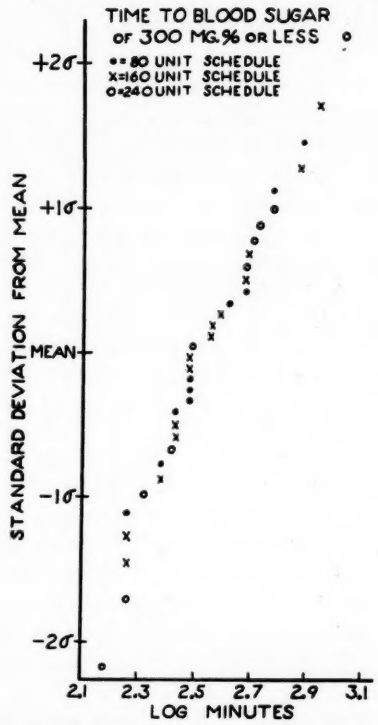

FIGURE 4. Distribution of cases in all three groups as to time required to lower blood sugar to 300 mg. per 100 cc. or less.

time required to reach this level. A second is that the first blood-sugar level less than 300 mg. may have been obtained some time after the blood sugar actually passed this level (at least variable times in the different cases). Finally, it might be expected that the higher the starting level of the blood sugar the longer it would require to reach any arbitrary level. None of these, however, is germane to the issue of the response of the blood sugar to insulin. This response can be directly studied since data are available relative to the time interval from each dose of insulin to each blood sugar value. Multiple graphic representations of the blood-sugar values against time were made, and it was found that a plot of the log of the blood-sugar value against the log of the time gave a good approximation of linearity in the great majority of individual cases. A regression was then computed on this linear basis. It is recognized that this might well fail to describe the results very early or very late beyond the limits covered by these data.

A regression coefficient, measuring rate of change of the blood sugar and not dependent in measurement on the initial blood-sugar value, was calculated for each patient prior to the administration of glucose, and the mean and standard deviation of the means of these regression coefficients was found for the various patient groups.

Comparing in this fashion survivors and fatalities, a t value of 0.27 carrying a probability of 0.8 was found. Comparing the mean regression values of the 80- to 160-, 80- to 240- and 160- to 240-unit groups, probabilities of 0.5, 0.15, and 0.2 were obtained. Finally the question as to whether the rate of blood sugar fall was related to blood-sugar level on admission was tested for survivors and deaths, for each treatment group and for all patients, and no correlation was found.

The average times required for the bicarbonate to reach 20 mEq/L. or more were 8.0, 8.0 and 7.4 hours, for the 80-, 160- and 240-unit groups respectively, as shown in Table 5, and although there appears to be some difference in favor of the 240-unit treatment schedule, Figure 5 graphically demonstrates the three dosage groups to be randomly distributed in a linear pattern.

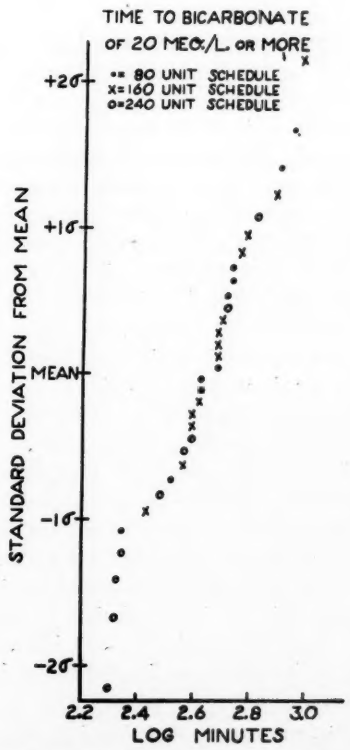

FIGURE 5. Distribution of cases in all three groups as to time to raise serum bicarbonate to 20 milliequiv. or more.

In a manner similar to that used in determining the rate of fall of the blood sugar, a regression study was made in each patient determining the rate of increase in the bicarbonate values. The probabilities attached to the differences between pairs of means for these regression rates for survivors and fatalities were in the 80-unit group 0.01, in the 160-unit group 0.05, in the 240-unit group 0.5, and for all survivors and all fatalities 0.01. In each instance the rate of bicarbonate rise was more rapid in the survivors than in the fatalities, and this difference appeared significant.

The probabilities for the differences between the means of the three treatment groups were from 0.3 to 0.8 for the survivors and from 0.2 to 0.9 for the deaths. For all patients in the several groups the p values were 0.4 to 0.8. These are all probabilities which one would expect to encounter in drawing multiple samples from the same population, and any difference observed could be ascribed to chance alone. No significant correlation was noted between the bicarbonate regression coefficient and the bicarbonate value on admission, or between the bicarbonate and blood-sugar regression coefficients.

One might suspect that increasing insulin dosage, all other factors being similar, would increase speed of recovery from the insulin deficit state of diabetic coma, and this would obviously be true in the low ranges of one or two units per hour not yet experimentally demonstrated. But there is undoubtedly a range in which marked increases in dosage do not greatly change effect. We believe that the area extending from 80 to 240 units for each two-hour interval is in this range, and we suspect that it extends a little below and a great deal above these limits. In support of this is that in an effective dosage range in which doubling and tripling the dosage has demonstrated no significant increase in effect, it is highly unlikely that multiplying the dosage five or ten times would produce a response not discernible in the lower area. In an unreported study of 116 severe coma cases of our own with admission bicarbonate levels of 6.8 mEq/L. or less and blood sugar levels of 700 mg. or more, there was no significant variation in the mortality of the groups receiving from 100 to 750 units of insulin during the first twelve hours of treatment, nor in fact any improvement in mortality by increasing the insulin dosage beyond 10 to 15 units per hour.

We believe that an analysis based on the principles used in this study of these three dosage levels would support this thesis if applied to published cases treated with dosage schedules on the order of five or ten times those used by us.

CAUSES OF DEATH

The mortality of 26 per cent during the 53 weeks of this study was considerably higher than we had experienced during 1949, 1950, and 1951, when the coma mortality was 11 per cent, 11 per cent, and 15 per cent for 62, 44, and 46 cases respectively. The only significant change in therapy instituted during this study was in insulin dosage. Previously all coma patients had initially received 40 units intravenously and 40 units subcutaneously, with subsequent doses varied accordingly to the change in the blood sugar.

It must be apparent that the causes of death commonly occurring in any large city or county general hospital will strike with similar frequencies among the nondiabetic and diabetic populations of such a hospital. Patients dying from these causes while simultaneously experiencing an episode of diabetic coma can properly be excluded from the mortality *of* diabetic coma, but should be included in the mortality data of patients dying *with* coincidental diabetic coma. We suggest that all data concerning deaths and diabetic coma be presented in this manner.

The eleven fatal cases in this study are presented in two groups. The first group (Table 6) comprises the 3 fatalities which we believe resulted from failure of treatment and should be classed as deaths due to diabetic coma, and possibly preventable.

TABLE 6

Deaths due to diabetic coma (treatment failures)

	Age	Sex	Duration of Treatment	Course and Cause of Death
80-unit group				
Case 1	61	F	12.5 hrs.	5-hr. delay in transfer; shock throughout; potassium 7 mEq/L. before death; autopsy showed bronchopneumonia, acute pyelonephritis.
Case 2	32	F	11.5	6 comas in 10 mos.; pulmonary edema and respiratory death; no intravenous fluids; potassium 4.5 mEq/L. before death.
240-unit group				
Case 3	31	M	18.5	Intoxicated; serum amylase 1300 units; blood pressure below 94/70 throughout; potassium 1.4 mEq/L. before death; died from respiratory failure.

It is obvious that in Cases 1 and 3 hypopotassemia was a major factor. We believe that the quantities of potassium recommended for our routine coma management would have sufficed. While it is possible that the bronchopneumonia and acute pyelonephritis in Case 1 and the shock in Case 2 would have resulted in death, the presence of these complications does not adequately reduce the responsibility for inadequate potassium therapy.

In Case 2 the coma was the sixth in ten months in a 32-year-old Negress who apparently died of respiratory failure and pulmonary edema. The serum potassium shortly before death was 4.5 mEq/L. All parenteral fluid was administered by clysis because of inability to get fluids to run properly by the venous route, because of thrombosis of the larger superficial veins resulting from previous recent coma therapy and no attempt being made at arterial or intrasternal infusion. However, intravenous therapy might have only hastened the occurrence of pulmonary edema and death. Shock did not appear until the last forty-five minutes of life.

There were eight deaths (Table 7) which we believe were not directly attributable to diabetic coma and except for Case 8 were in no way related to failure of the coma treatment.

The first case was that of a 64-year-old woman in coma some fifteen to thirty hours before admission, whose blood pressure remained below 74/40 for five hours before death despite all the supportive means noted in the table protocol. She was in a satisfactory state as to blood sugar and serum bicarbonate levels, and the serum potassium level of 2.9 mEq/L. was not in our experience sufficiently low to cause significant respiratory or cardiac embarrassment. The serum amylase of 1780 units very likely is indicative of acute pancreatitis. The second and third cases were previously unknown diabetics who entered in deep coma and were found at autopsy to have necrosis of the renal papillae and lung abscess, and an infarct of the entire small bowl, respectively. The fourth case was a previously unknown diabetic with a typical history of lobar pneumonia who remained in shock throughout the twenty hours of her treatment. She died apparently of the pneumonia and heart failure after making a rather good chemical recovery. The fifth patient was also a previously unknown diabetic who developed coma on a surgical ward while undergoing treatment for multiple stab wounds of the head, neck and chest and died of a massive intratracheal hemorrhage after chemical recovery from the coma. The sixth, a 60-year-old woman, made a rapid chemical and physical recovery from her coma but did not respond mentally and refused all oral feedings. Her death four and one-half days later from pulmonary edema and effusion resulted from administration of ex-

TABLE 7
Deaths due to complications

	Age	Sex	Duration of Treatment	Course and Cause of Death
160-unit group				
Case 1	64	F	15.5 hrs.	Coma 15-30 hrs.; white-cell count 2900; serum amylase 1780 units; intra-arterial blood infusion; i.v. venoxyl, neosynephrine; blood pressure <74/40 for 5 hrs. before death; blood-sugar level 343 mg./100 cc.; serum bicarbonate level 30 mEq/L.; potassium 2.9 mEq/L. before death.
Case 2	58	F	2.5 hrs.	Previously unknown diabetic; urine sediment negative; autopsy showed necrosis of renal papillae, lung abscess.
Case 3	83	F	19 hrs.	Unknown diabetic; hgb. 17 gm.; always in shock; autopsy showed infarct of entire small bowel.
Case 4	52	F	20 hrs.	Unknown diabetic; chills, fever, pleurisy; always in shock; chemical recovery; died from heart failure and pneumonia.
Case 5	47	M	6.5 hrs.	Unknown diabetic; chemical recovery from coma; autopsy showed intratracheal hemorrhage from stab wounds.
Case 6	60	F	4.5 days	Recovered from coma; refused oral feedings; given intravenously; autopsy showed pulmonary edema and effusion, 40-gm. pancreas.
240-unit group				
Case 7	27	M	5 hrs.	Found unconscious; shock; bilateral active pulmonary tuberculosis.
Case 8	48	F	5.5 hrs.	Alcoholic; always in shock; anuric; terminal bicarbonate 17 mEq/L.; potassium 1.3 mEq/L.; autopsy showed lobar pneumonia, interstitial pancreatitis, inflamed periportal triads of liver.

cessive parenteral salt and fluid. The seventh and youngest patient was an escapee from a tuberculosis sanitarium who was found unconscious and died without recovery from shock with bilateral diffuse active pulmonary tuberculosis. The eighth patient according to the autopsy examination died of lobar pneumonia, interstitial pancreatitis, and inflammation of the hepatic periportal triads. However, it should be noted that she was also in a state of severe hypopotassemia, anuria, and shock, and from these standpoints might also be classed as a case of treatment failure. Our experience with these diseases found at autopsy, however, leads us to believe death would have occurred even if chemical recovery had been brought about.

The corrected mortality, then, (the mortality due only to diabetic coma) is 7 per cent.

SUMMARY

1. Forty-three consecutive episodes of diabetic coma were treated as similarly as possible as to sodium, potassium, chloride and fluid intake, but were divided by lot into three groups in regard to insulin therapy. Twelve patients received 80 units, 18 received 160 units, and 13 received 240 units of insulin intravenously initially, and similar doses subsequently at approximately two-hour intervals until the blood sugar fell to such levels as to necessitate alteration in dosage.

2. The gross mortality was 26 per cent and the mortality due to diabetic coma and its complications was 7 per cent. The largest single cause of death was hypopotassemia.

3. Statistical analysis of the data demonstrated that changes in the insulin dosage from 80 to 160 to 240 units every two hours failed to influence the duration of clinical diabetic coma, the time required to lower the blood sugar to 300 mg. or less, or the time required to raise the serum bicarbonate level to 20 mEq/L. or more. There was no significant difference among the three dosage groups in the rate at which the blood sugar fell or the rate at which the serum bicarbonate rose.

ACKNOWLEDGMENT

We wish to express our appreciation to Frederick J. Moore, M.D., Professor of Experimental Medicine, University of Southern California School of Medicine, for suggestions and statistical analysis of the data.

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DISCUSSION

ALEXANDER MARBLE, M.D., (*Boston*): Drs. Smith and Martin are to be congratulated on having carried through a program of clinical investigation in which there were many different participants. This is certainly an achievement as anyone who has attempted this sort of thing will attest.

The results are most instructive and bear out the clinical impression that in the average case of diabetic acidosis and coma, there comes a point at which with increasing dosage of insulin, the law of diminishing returns operates. From the standpoint of clinical research, the contribution of Drs. Smith and Martin is most important and valuable. However, if a similar technic were carried over into the routine management of diabetic coma by physicians everywhere, certain patients would be lost who otherwise might recover. The reason for this is that in actual practice there is no such thing as an "average" patient. Each case presents its own problems which must be handled individually.

In order to illustrate what I mean, let me take two extremes. On the one hand, let us suppose that we have adopted a schedule calling for 80 units of insulin initially with 80 units or less every two hours depending upon the behavior of the blood and urine tests for sugar. If there happened to appear a patient with coma of unusual severity or of unusual duration prior to admission or with whom for one reason or another insulin resistance was extremely marked, such a patient might die before enough insulin was administered. Thus a patient who, with management of the ordinary type might require 1000-2000 units of insulin for recovery, would have received only 320 units at the end of 6 hours. On the other hand, let us suppose that we are following a schedule calling for 240 units initially and 240 units or less every two hours. Let us suppose that a patient is presented whose age is below that covered in the series by Drs. Smith and Martin, say a child, age 8 or 10 years, and that diabetes is of recent onset. Even the initial dose of 240 units would represent such an excess that one might well have considerable difficulty in keeping the child out of dangerous hypoglycemia even with the constant infusion of glucose.

The above is not intended as a criticism of the work just presented provided it is regarded as clinical research. As far as actual practice is concerned, it would appear wisest to individualize treatment and to gauge the dosage and time of administration of insulin, the administration of fluid and electrolytes and other measures according to the particular needs of the individual patient. There are many factors which affect the insulin needs in the patient with diabetic coma. These include age, duration of the diabetes, type of previous treatment and the presence of complications. In our own group, we have come to believe over the years that large doses of insulin given initially provide for a more prompt and sure recovery from diabetic coma than do smaller doses given at intervals over a period of 6 to 12 hours. We believe that determination of the blood sugar at intervals of 2 to 3 hours during the early hours of treatment provides an excellent basis for evaluating the insulin needs of the patient under treatment. In recent years we have learned the great value of the semiquantitative test of the plasma acetone on the initial blood sample as a rough guide to insulin needs. This information can be obtained within five minutes of the time of first seeing the patient and long before values for blood sugar and carbon dioxide content are available.

Although in our group we try to use potassium either parenterally or orally as indicated in the individual case, we believe in exercising great caution unless the urinary output is thoroughly adequate.

I agree with Drs. Smith and Martin that in a presentation of results of treatment of cases of diabetic coma, it is instructive to indicate those in which it seems reasonably certain that death was not due to the acidosis but to complications. However, it would be most unwise if all deaths in any given series were not reported. Otherwise, it becomes too easy to stray from acceptable standards. It is our own policy to report as a death from diabetic coma, any case in which the patient enters in diabetic coma and does not leave the hospital alive.

KENDRICK SMITH, M.D., (*Los Angeles*): It is a privilege to have such a well-known authority on coma as Dr. Marble to discuss this paper, and I very much appreciate, and I know Dr. Martin does, his very kind words.

Frankly, we undertook this study in an effort to find out if we were using large enough doses of insulin since they differed very widely from those published in the literature. I must say that we were surprised that we were unable to demonstrate any significant statistical difference in the outcome based on these data.

I must say that prior to the statistical evaluation of the data, it seemed that the 240-unit schedule was much more effective than either of the other two. This impression was not confirmed, however, under close scrutiny. However, I am still sure that all of us as clinicians would be inclined to use as large or as small doses of insulin as we think needed in the individual case.

Sodium Content on Dietary Food Labels

New regulations under the Federal Food, Drug, and Cosmetics Act, requiring the labels of "salt free" or "low sodium" food products for dietary use to declare sodium content in milligrams of sodium per 100 mg. of the food and per average serving, will go into effect on September 29, 1954. The "average serving" is required to be expressed in common terms, such as number of slices, cookies, or wafers, or in cupfuls, tablespoonfuls, or teaspoonfuls.

In recent years, the increase in packing of special foods for persons suffering from high-blood pressure and certain types of heart, liver, and kidney diseases has been accompanied by variation and confusion in labeling terminology. Many products labeled "salt free" or "no added salt" contained substantial amounts of sodium, sometimes naturally present in the food, sometimes added in the form of baking powder or other ingredients.

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An Approach to the Prediction of Diabetes Mellitus by Modification of the Glucose Tolerance Test with Cortisone

Stefan S. Fajans, M.D., and Jerome W. Conn, M.D., Ann Arbor, Michigan

A large proportion of presently nondiabetic individuals who have a family history of diabetes mellitus will eventually manifest the disease. If one could separate those who harbor the potentiality for diabetes from those who do not, further study of inciting factors would be possible. It is conceivable that impairment of reserve islet-cell function may exist in such individuals even though carbohydrate tolerance can be demonstrated to be normal at the present time.

The present study was begun in 1950 with the following objectives: to attempt to unmask the potential diabetic who manifests normal carbohydrate tolerance by present testing methods; and to determine whether or not the established diabetogenic activity of corticotropin and/or cortisone could be used to bring to the surface a subclinical defect in the metabolism of carbohydrate.

It became necessary, as the initial step in this investigation, to establish a single testing dose of either corticotropin (ACTH) or cortisone which would not modify significantly carbohydrate tolerance in people with no family history of diabetes, but which *would modify significantly* carbohydrate tolerance of a considerable number of individuals with known family histories of diabetes mellitus. This has been accomplished and forms the basis of one of our major findings, namely, that 24 per cent of presently nondiabetic relatives of diabetics react to this test in a specific way, while this same response is observed in the control group in but 3 per cent of subjects. As will be detailed below, the total dose of cortisone employed in this test is 100 or 125 mg. of cortisone administered orally as two doses during an eight and one half-hour period prior to the oral glucose tolerance test.

Presented at the Annual Meeting of the American Diabetes Association in San Francisco on June 20, 1954.

From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.

METHOD OF INVESTIGATION

Subjects

Glucose tolerance tests were performed before and after the administration of corticotropin or cortisone in 152 ambulant, healthy relatives of diabetic patients and in 50 normal control subjects without a known family history of diabetes. The relatives of diabetics were offspring, siblings, or parents of patients with diabetes. Of the 152 individuals, there were 58 males and 94 females. The males ranged in age from 10 to 67 years, with a mean of 30 years. The females ranged in age from 10 to 65 years, with a mean of 33 years. Medical students, physicians, dietitians, and other healthy individuals, each without a known family history of diabetes, were used as control subjects. The control series included 27 males (range 18 to 66 years, mean 28 years) and 23 females (range 18 to 57 years, mean 29 years).

Glucose Tolerance Tests

For three days preceding the first (base line) glucose tolerance tests, all subjects ingested a standard preparatory diet containing 300 gm. of carbohydrate.[1] The oral glucose tolerance test was employed using 1.75 gm. of glucose per kg. of ideal body weight, calculated from the subject's height and age. Venous blood was obtained in the fasting state and every half-hour for three hours after the ingestion of glucose. The blood sugar was determined in duplicate by the Nelson modification of the Somogyi method,[2] yielding "true blood sugar" values.

After completion of the base line glucose tolerance tests the subjects continued on their standard preparatory diets for lunch and dinner of that day. The next morning the second glucose tolerance test was done. This time, however, the subjects received the priming doses of cortisone.* If the subject weighed less than 160 lb. he

*We are indebted to the Upjohn Company, Kalamazoo, Mich., and to Merck & Company, Rahway, N.J., for the cortisone acetate used in these studies.

received orally 50 mg. of cortisone acetate eight and one-half hours and two hours preceding the ingestion of glucose. If he weighed more than 160 lb. he received 62.5 mg. of cortisone acetate orally at the same time intervals. The total number of subjects finally tested in this specific way was 130 (37 controls, 75 non-diabetic relatives of diabetic patients, and 18 diabetics). Not included in the present report are data obtained with ACTH or with varying amounts of cortisone. However, base line data ("unprimed" glucose tolerance tests) from the entire group (202 subjects) are recorded (figure 1) for the purpose of indicating the incidence of undetected diabetes among apparently healthy relatives of diabetic patients.

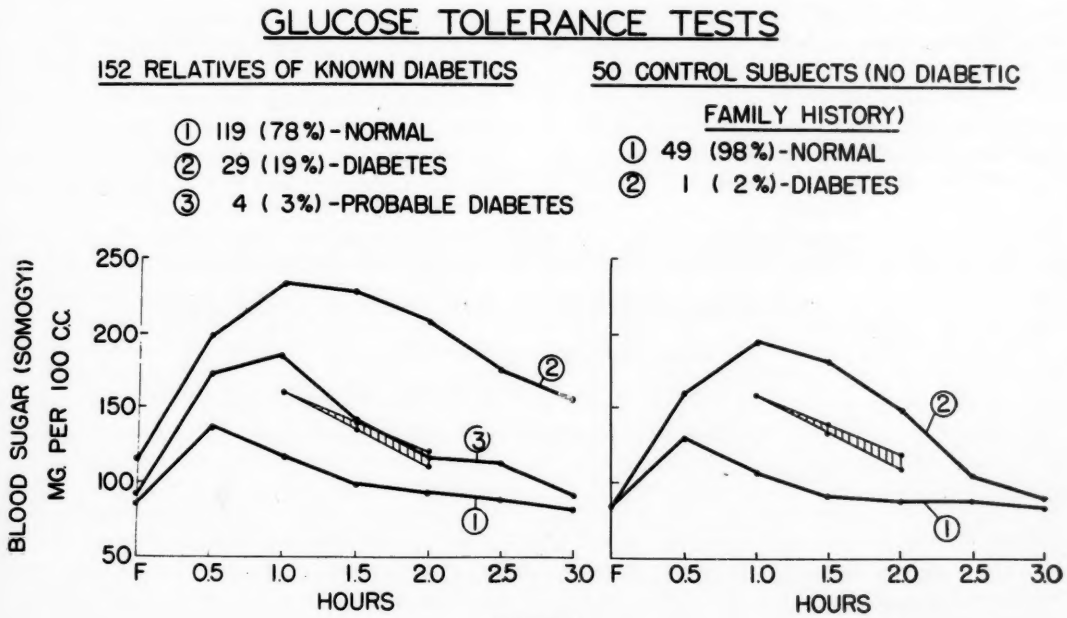

FIGURE 1

Interpretation of Glucose Tolerance Test

The criteria employed for the interpretation of the initial (pre-cortisone) glucose tolerance test were similar to those of Mosenthal and Barry[3] and of Moyer and Womack.[4] These, as well as most other investigators, consider the two-hour blood sugar value as the critical one. Mosenthal, employing the "true blood sugar" method on venous blood in ambulant individuals, established the following criteria as indicating normal carbohydrate tolerance: fasting, 100 mg. per 100 cc. of blood or less; a maximum height of the curve of 150 mg. per 100 cc. or less; and a level of 100 mg. per 100 cc. or less two hours after the ingestion of glucose. Diminished carbohydrate tolerance was indicated when both the peak of the blood-sugar curve and the two-hour value were elevated.

Moyer and Womack employed the Folin-Wu blood sugar method, which gives blood sugar values averaging approximately 20 mg. per 100 cc. higher than those obtained by the Somogyi method. The criteria for a normal test used by Moyer and Womack were a fasting blood sugar of 120 mg. per 100 cc. and a two-hour blood sugar of 120 to 125 mg. or less. Two-hour blood sugar values between 125 and 140 mg. were regarded as presumptively abnormal, and levels above 140 mg. as definitely abnormal or diabetic. The height of the curve was thought to be of little diagnostic significance.

Using the standard preparatory diet and the Somogyi blood-sugar method, we regard the combination of a one-hour value of 160 mg. per 100 cc. or above plus a two-hour value of 120 mg. or above as diagnostic of the existence of the diabetic state. A diagnosis of probable diabetes was made when the one-hour value exceeded 160 mg. and the two-hour value fell between 110 and 120 mg. In order to eliminate a false diagnosis of diabetes on the occasional curve which drops abruptly at 1.5 hrs. and rebounds above 120 mg. by two hours, we have added a third criterion, namely, that the level

at 1.5 hrs. be 140 mg. per 100 cc. or above to be diagnostic. Figure 1 illustrates these criteria. A diabetic curve is one in which all points lie at or above the upper border of the crosshatched triangle. A probable diabetic curve is one which lies at or above the lower border of the crosshatched zone but in which the sugar level at two hours is between 110 and 120 mg. per 100 cc.

We are convinced that when standard dietary preparation is employed and "true blood sugar" is measured these criteria are sound. Nevertheless, some will regard them as insufficient evidence on which to base a diagnosis of diabetes mellitus. If this can be proved, then our figures for incidence of fully developed, undetected diabetes in relatives of diabetics would be too high. It is equally clear, however, that those relatives of diabetics whose tolerance curves fall below these levels would be called diabetic by no one. It is this specific group, which would not be called diabetic by any presently accepted criteria, that makes up the main interest of this communication. Can this group be split into two categories, one potentially diabetic and the other not?

RESULTS

Figure 1 shows the incidence of diabetes in subjects with and without a family history of diabetes. In the group of 152 relatives of diabetics 29 (19 per cent) were found to be diabetic on the initial test. This represents the incidence of unsuspected diabetes in this group. Using the same criteria in the control group only one (2 per cent) of 50 could be called diabetic.

Four more subjects (3 per cent) with positive family histories gave curves indicating probable diabetes, while none in the control group had borderline curves. On figure 1 are shown the composite curves for these groups.

In 37 of 49 normal control subjects (figure 2) the cortisone-glucose tolerance test (described under Methods) was performed. One individual showed a high curve (curve 3) and 36 gave low curves (composite curve 2). The mean two-hour blood-sugar value of these 36 subjects was 103 mg. per 100 cc. with a standard deviation of 12.4 mg. Using three standard deviations from the mean as representing a high degree of significance, we arbitrarily set a level of 140 mg. per 100 cc.

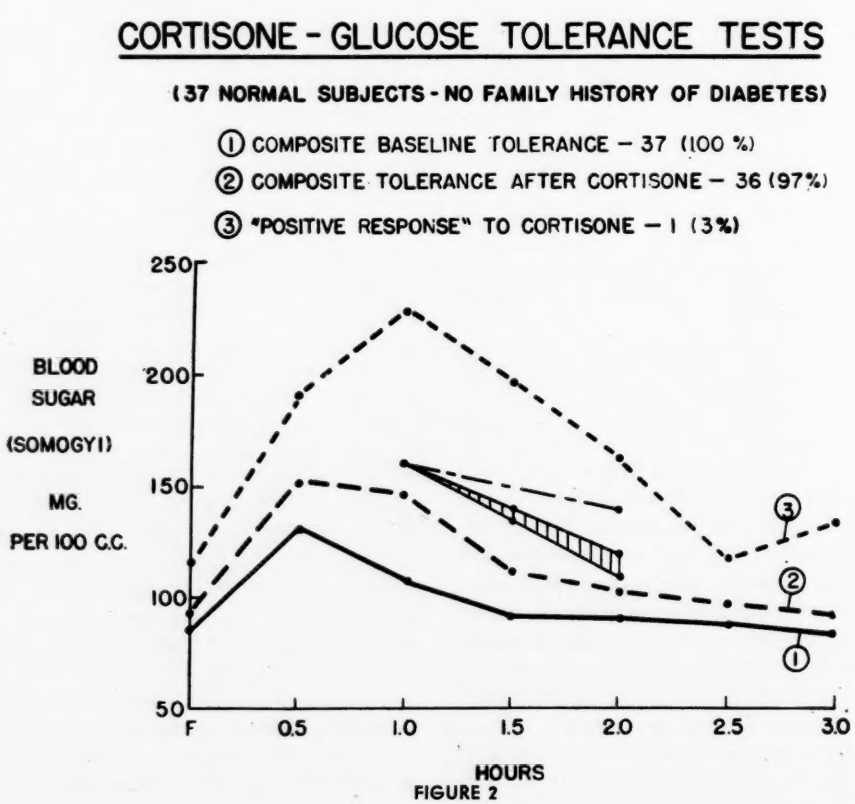

FIGURE 2

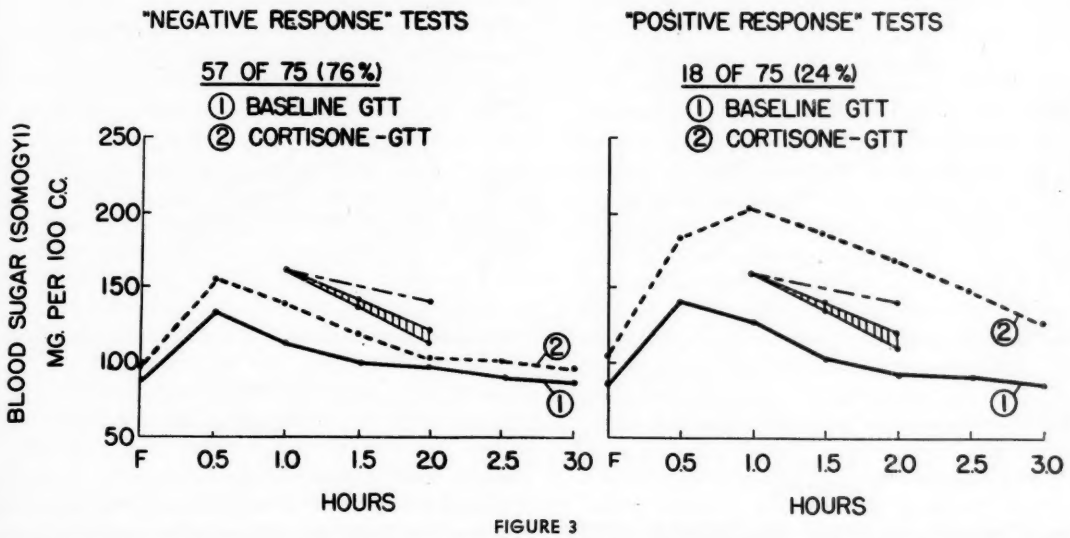

FIGURE 3

(103 plus 37) at two hours as the critical one for interpretation of the cortisone-glucose tolerance test. Thus a cortisone-glucose tolerance curve giving a two-hour blood sugar level of 140 mg. or above represents a positive response, while one below 140 mg. is, for present purposes, regarded as a negative response. In the various figures the broken line which connects a one-hour value of 160 mg. per 100 cc. with a two-hour value of 140 mg., defines our criteria for a positive or negative cortisone-glucose tolerance test. Figure 2, then, shows the composite base line glucose-tolerance tests for the 37 control subjects, the composite cortisone-glucose tolerance tests in the 36 individuals (97 per cent) with negative responses, and the curve for the one subject (3 per cent) with a positive response.

Cortisone-glucose tolerance tests were performed on 75 persons with a family history of diabetes but whose base line glucose tolerance tests were *normal* (figure 3). Of the 75 individuals, 57 (76 per cent) showed a negative response and a mean two-hour blood sugar level of 104 mg. per 100 cc. This level is the same as that seen in 97 per cent of the control subjects during the cortisone-glucose tolerance test. Eighteen of the 75 (24 per cent) showed a positive response and a mean two-hour blood sugar level of 169 mg. It is interesting, at this point, to observe that 32 per cent of those who gave a negative response and 11 per cent of those who gave a positive response were more than 15 per cent overweight.

Cortisone-glucose tolerance tests were done on some of the subjects who were discovered to have diabetes on the initial glucose-tolerance test. Figure 4 shows the composite base line and cortisone-glucose tolerance tests of 12 previously unsuspected diabetics. The mean two-hour blood-sugar level of the base line tests was 170 mg. per 100 cc. It rose to 217 mg. during the cortisone-glucose tolerance test. Two of the 12 diabetics showed no further elevation of the blood-sugar level over base line values during the cortisone test.

Figure 5 shows the composite curve of three subjects classified by their initial glucose tolerance test as probable diabetics. The cortisone-glucose tolerance test was positive in all three, with a mean two-hour blood sugar level of 188 mg.

Figure 6 demonstrates data obtained in six obese, mild diabetics. Curve 1 shows the composite base line glucose tolerance at the time of the initial test. These patients were then fed low-calorie diets and lost from 15 to 30 lb. of body weight. All of the six patients then exhibited normal glucose tolerance curves (curve 2). Cortisone-glucose tolerance tests were now performed. All demonstrated their defect by giving a positive response (curve 3). This latter curve is similar to that obtained in 24 per cent of people with family histories

of diabetes whose base line glucose tolerance curves are normal (figure 3).

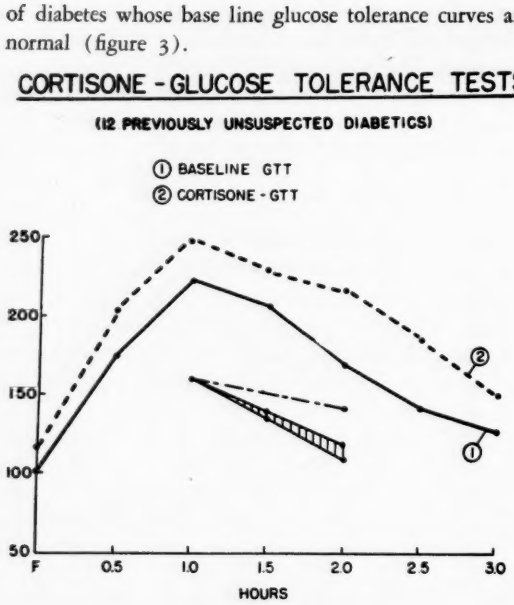

FIGURE 4

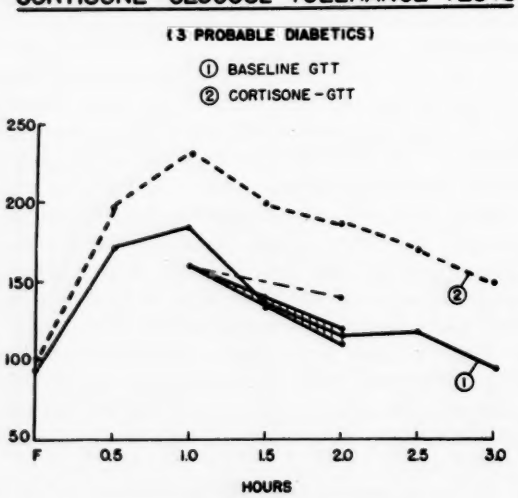

FIGURE 5

DISCUSSION

This study was initiated to determine whether the potentiality for the development of diabetes could be uncovered in presently *nondiabetic* relatives of diabetic patients. It was surprising indeed to find that at least 19 per cent of apparently healthy relatives of diabetic patients were already diabetic by the same criteria that gave an incidence of 2 per cent in people without a known family history of diabetes.

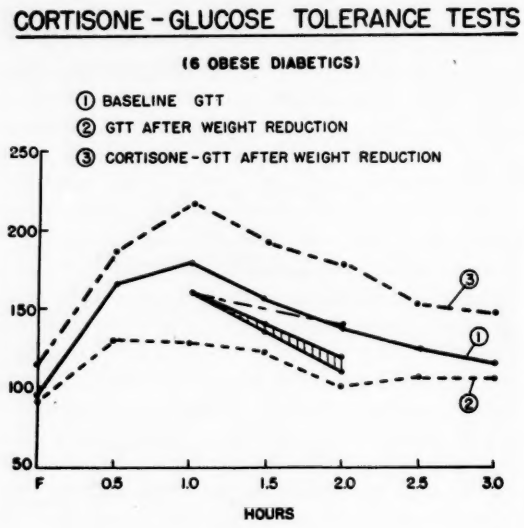

FIGURE 6

Neel[5] has summarized the literature pertaining to the incidence of diabetes as determined by glucose tolerance tests in relatives of diabetic patients. He found that in the various studies the incidence of unsuspected diabetes varied from 0 to 72 per cent of the groups tested. The wide difference in the results of these various investigators are accountable on the basis of (1) varying criteria for what constitutes an abnormal glucose tolerance curve, (2) lack of awareness of the importance of standard dietary preparation, and (3) lack of adequate control studies. We believe that our figure of 19 per cent (or possibly 22 per cent) is highly significant. A detailed genetic analysis of the relation between the incidence of newly discovered diabetes and family background, as observed in our series, will appear in a separate communication.

With respect to possible detection of potential diabetes in the presence of normal carbohydrate tolerance by present testing methods, it seems very significant that 24 per cent of 75 nondiabetic relatives of diabetic patients show a response to the cortisone-glucose tolerance test, which is distinctly different from the rest of that group, and that this abnormal response was observed in but 1 of 37 (3 per cent) control subjects. It is important, too, that the abnormal cortisone-glucose tolerance response exhibited by 24 per cent of nondiabetic relatives of diabetics is the same response given by (1) the group with established diabetes, (2) the group with probable diabetes, and (3) the group of obese diabetics

whose carbohydrate tolerance had returned to normal after reduction of body weight.

The remaining 76 per cent of nondiabetic relatives responded to the cortisone-glucose tolerance test, as did 97 per cent of the normal controls with but minimal loss of carbohydrate tolerance.

Thus, on the basis of rigidly controlled experiments a test has been devised which separates into two distinct groups the presently nondiabetic relatives of diabetic patients. One group responds to this test as diabetics do, and the other group responds as do the controls. Only the future incidence of clinical diabetes in the two groups, as well as in the control group, can prove whether or not the cortisone-glucose tolerance test as used in these studies has value in predicting which nondiabetic members of a family tainted with the disease will eventually manifest it themselves. Such serial studies are already in progress, but it probably will be many years before a definite answer becomes available. In the meanwhile the total series continues to be enlarged and work continues in several directions. Further study is needed, for example, of varying dose-time schedules with respect to administration of carbohydrate-active steroids. Insufficient steroid activity at a given time may fail to disclose some subjects with a diabetic diathesis while excessive activity results in significant loss of carbohydrate tolerance in normal individuals.

One study has been reported in which the use of a corticotropin-glucose tolerance test was employed for the detection of potential diabetes. Berger[6] performed glucose tolerance tests before and after administration of corticotropin to 12 patients (over age 50) with known diabetes, 14 siblings (over age 50) of known diabetics and 24 *patients* (18 over age 50, 6 under age 30) without diabetes or a family history of diabetes. One hundred milligrams of corticotropin were given subcutaneously one hour before the second test. Following administration of ACTH, all patients with known diabetes, all siblings of diabetics, and two of the 24 patients without a family history of diabetes (one over age 50, one under age 30) showed a significant loss of carbohydrate tolerance. The blood sugar method employed and use of a dietary preparation preceding the tests were not commented on. The composite control glucose tolerance curve of the 14 "normal" siblings of diabetics shows a mean fasting blood sugar of 100 mg. per 100 cc. and a mean two-hour blood sugar of about 200 mg. Several or all of these individuals must have had diabetes mellitus. Furthermore, the composite control glucose tolerance curve of the 18 control "nondiabetics," without a family history of diabetes, shows a mean fasting blood sugar of approximately 150 mg. per 100 cc. and a two-hour blood-sugar level of almost 200 mg. The composite control curve for the 6 young nondiabetic patients without a family history of diabetes shows a mean fasting blood sugar of approximately 125 mg. per 100 cc. and a two-hour blood-sugar level of about 150 mg. Such information cannot be evaluated.

Finally, one can merely speculate upon the possible mode of action by which the cortisone-glucose tolerance test separates into two groups the presently nondiabetic relatives of diabetics. It has been suggested by three groups of investigators[7-9] that normal islets of Langerhans respond with increased function to the hyperglycemic effect of adrenal corticosteroids. When Zucker[7] gave subdiabetogenic amounts of alloxan to rabbits, small doses of adrenal cortical extract, which failed to modify carbohydrate tolerance in normal rabbits, produced significant impairment of carbohydrate tolerance. Hoet[10] has found that pregnancy is attended by only a slight loss of carbohydrate tolerance in the normal rabbit. However, in rabbits which have received subdiabetogenic doses of alloxan and in which no modification of carbohydrate tolerance is discernible, pregnancy leads to a transient diabetic state. Pregnancy has been shown, of course, to be associated with an increase in the level of 17-hydroxycorticosteroids in blood[11] and in urine.[12-13] While far from proved, it may be that an insulogenic mechanism with marginal reserve function is sufficiently taxed by a small but sudden excess of 17-hydroxycorticoid activity that it temporarily decompensates.

SUMMARY

Glucose tolerance tests have been done on 152 ambulant, healthy relatives of diabetic patients and on 50 normal control subjects who had no known family history of diabetes. All subjects consumed a standard diet prior to each test. "True blood sugar" was measured.

Unsuspected diabetes was found in at least 19 per cent of 152 relatives of diabetic patients. Only one of 50 control subjects demonstrated a diabetic glucose tolerance test.

Studies on the *nondiabetic* relatives of diabetics comprised the major effort of this investigation. Glucose tolerance tests were repeated in 130 individuals (37 controls, 75 nondiabetic relatives of diabetics, and 18 diabetics) after oral administration of 100 or 125 mg. of cortisone during an eight and one-half hour period immediately preceding the second test. Twenty-four per cent of the nondiabetic relatives of diabetics showed marked loss of carbohydrate tolerance during the cortisone-glucose tolerance test. Only one of the 37 controls

showed a similar loss of carbohydrate tolerance.

Ten of 12 known diabetic patients showed further significant loss of carbohydrate tolerance during the cortisone-glucose tolerance test.

Six obese diabetics consumed submaintenance diets until they had lost from 15 to 30 lb. of body weight. After reduction of weight they all exhibited normal carbohydrate tolerance by the standard test. At this time, however, all six patients gave the same response to the cortisone-glucose tolerance test as that obtained in 24 per cent of nondiabetic relatives of diabetics.

Thus, it has been possible by means of this test to separate into two distinct groups the presently nondiabetic relatives of diabetic patients. Those who exhibit a positive response (24 per cent) react to the test as known diabetics do. The rest give the same response to the test as that which is obtained in 97 per cent of the control group which has no known family history of diabetes. Serial studies of these individuals over the coming years will determine whether those who give a positive response are indeed those who comprise our future diabetic population.

The necessity for rigid control of this type of investigation has been emphasized.

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DISCUSSION

RANDALL G. SPRAGUE, M.D., (*Rochester, Minn.*): Dr. Fajans has asked me to open the discussion of the paper by Dr. Conn and himself. This I am glad to do, because I regard their paper as a rather important study which has significant practical and theoretical implications. Incidentally, it brings out an important point regarding the conduct of a study involving glucose tolerance tests; namely, the importance of use of a standard preparation for such tests with a high carbohydrate diet in order to avoid false positive results.

The use of cortisone as described by the authors gives promise of being an accurate method for recognition of the state of individuals who have the potentiality for the development of diabetes. Thus, a new field of study of the various factors existing in the individual before the development of frank diabetes is opened up, and it also becomes possible to study various inciting factors.

Early in the days of cortisone and corticotropin, many observers noted that diabetes occasionally is precipitated by the administration of these hormones. My associates and I noted some time ago that in an individual with a family history of diabetes, cortisone may precipitate diabetes, whereas in other individuals without a family history of diabetes, it does not do so. However, this work of Fajans and Conn is the first really systematic study of the problem, and it provides a mass of significant data indicating that cortisone is much more likely to precipitate diabetes in individuals with diabetes in their families than in those without diabetes in their families.

We all know that stress of various sorts may either precipitate diabetes or intensify existing diabetes. Cortisone is a readily administered and easily controllable form of stress, you might say, and it is not surprising that it should be capable of inducing diabetes in susceptible individuals. One aspect of the study that surprised me, however, was the small dose of cortisone that was required. I should like to ask Dr. Fajans how extensively he explored the matter of dosage before he arrived at this particular dose of 100 to 125 mg. given a short time before the tolerance tests were performed.

An interesting by-product of the study is the observation that approximately one of five relatives of known

diabetics has a demonstrable impairment of carbohydrate tolerance without the administration of cortisone. For those who are interested in the practical problems of detection of diabetes, this observation points out a group toward which detection efforts can be directed profitably.

There are only two other comments I should like to make. I wonder if further control of the study might have been exercised by study of the effects of inert tablets, instead of cortisone, on the results of glucose tolerance tests in order to rule out the possibility of any psychic effect of the administration of tablets. Last, I should like to ask Dr. Fajans what he tells the patients in whom he demonstrates impairment of carbohydrate metabolism after the administration of cortisone. In other words, in practical terms, how does he apply the information gained from this type of study?

GEORGE E. ANDERSON, M.D., (*Brooklyn*): At the State University of New York, we have been investigating preclinical detection of predisposition to diabetes by means of a test to determine the promptness of the individual's responsiveness to glucagon-free insulin.

We have been doing this on medical students because we realize we shall be able to follow them for the rest of their lives through the AMA—at least, most of them. We are particularly pointing to the ones who have a family history of diabetes. In many of these we find that before any positive evidence of faulty insulin function can be demonstrated by a glucose tolerance test and abnormal postprandial blood sugars, there is exhibited an inability to respond normally to insulin. Some of them show no early responsiveness at all to glucagon-free insulin.

I should like to see this type of study correlated with the present very excellent one on preclinical detection.

We are carrying out the same test in obese nurses. We shall in them, of course, not be able to follow up as readily. We find in a significant percentage of these that there is an inability to respond as does the normal individual to glucagon-free insulin.

JOHN A. REED, M.D., (*Washington, D.C.*): Dr. Fajans, have you made a similar study on obese individuals without a family history of diabetes?

W. Q. WOLFSON, M.D., (*Detroit*): Because of the increasing use of the carbonic anhydrase inhibiting diuretic, Diamox, which always causes increased excretion of potassium, and because of the possible importance of potassium depletion in precipitating steroid diabetes, a recent experience of ours may be of some interest.

The patient was a Negro girl with severe acute posterior uveitis under treatment with ACTH; she also had mild narrow-angle glaucoma. During hormone therapy, she remained normoglycemic and aglycosuric until she was given Diamox for 8 hours to reduce her intraocular tension. Tremendous glycosuria appeared during its use and persisted thereafter. Except on one fractional sample, there never was significant ketonuria, but her diabetes was so insulin-resistant that on 80 units of ACTH and 160 units of NPH insulin daily, she continued to lose up to 300 gm. of glucose in the urine daily. Because this situation seemed medically unstable, systemic therapy was discontinued and the eye condition was controlled with intra-vitreous hydrocortisone. She again became normoglycemic and aglycosuric about one month later.

This girl unquestionably had a predisposition to steroid diabetes since her mother has clinical diabetes mellitus. Nevertheless, the relationship to the use of a known potassium-depleting diuretic was so impressive that we feel that, for the present, it is probably advisable to withhold Diamox from patients receiving treatment with cortisone, hydrocortisone, or corticotropin.

FRANK L. ENGEL, M.D., (*Durham, N.C.*): I should like to make one or two observations about this interesting study of Drs. Fajans and Conn. A few years ago we studied the effect of cortisone on the glucose tolerance and insulin sensitivity comparing healthy individuals (medical students) with patients in the hospital who were unselected, except that they did not have any history of diabetes. When these individuals were given 200 mg. of cortisone and either a glucose or an insulin tolerance test was done four hours later the ill patients invariably showed impaired tolerance tests, while normal, healthy students showed no abnormal response after the cortisone. This means that when one uses the very interesting technic of Drs. Fajans and Conn, the results must be interpreted with caution if the patient is suffering from any active illness at the time of the test.

DAVID ADLERSBERG, M.D., (*New York*): I would like to ask only whether cortisone was evaluated versus corticotropin in preparing these patients for the glucose tolerance tests.

I am asking this question because of our observations on steroid diabetes in non-diabetics who have received in contrast to the technic used by Fajans and Conn, for *prolonged* periods of time cortisone or ACTH for the treatment of their basic disease. We presented this study two years ago before the Association. In four of five patients administration of cortisone for prolonged periods of time had no diabetogenic effect, while replacement of cortisone by ACTH resulted in glycosuria

and hyperglycemia. My question is then how does ACTH compare with cortisone in your studies the purpose of which is "prediction of diabetes," I realize.

STEFAN S. FAJANS, M.D., (*Ann Arbor, Mich.*): I should like to thank all of the discussers for their remarks. I would also like to thank Dr. Sprague especially for opening the discussion and for his very kind remarks.

We did explore other dosage schedules, Dr. Sprague. As a matter of fact, there is need for further study of varying dose-time schedules with respect to administration of carbohydrate-active steroids. We found that insufficient steroid activity at a given time may fail to disclose a diabetic diatheses in some subjects who give a positive response by the present technic. Excessive steroid activity on the other hand results in significant loss of carbohydrate tolerance even in some normal controls. We arrived at the present dosage schedule after experimenting with various dosages of corticotropin and cortisone for almost three years.

We did not use inert tablets for control because, as I just mentioned, a dosage which was too small gave no response while the present dosage gave a positive response in the same individuals.

What do we tell the individuals who have normal glucose tolerance tests but who show a positive response to our test? We tell them they need a prolonged follow-up. We do not tell them they are diabetics. We tell them that they may possibly develop diabetes in the future and therefore, they should have routine follow-up studies at six-to-twelve-month intervals. This is one way in which we hope to prolong our study and to reach a conclusion concerning the value of the test.

Dr. Reed, we did have some obese individuals in our control group. They did not respond differently from the controls of normal weight. In the nondiabetic individuals with a known family history of diabetes one interesting fact came out. Among the individuals who gave a positive response there was a smaller incidence of obesity, namely 11 per cent, than among the individuals with negative responses 32 per cent of whom were more than 15 per cent overweight. This is just the reverse of what one might expect.

Dr. Engel, I am well aware of your excellent study. As I remarked at the beginning, all the subjects were ambulant, healthy individuals. We did not use any individuals who were hospitalized.

Dr. Adlersberg, we did use ACTH (corticotropin) initially. We got varying responses because of variations in the batches of ACTH, but also individual variations with the same ACTH. Since there may be variations in adrenal responsiveness to the same dose of ACTH, we discontinued the use of ACTH in our testing method.

Actually we were not interested in producing steroid diabetes, as steroid diabetes is usually defined, but simply in the elicitation of this abnormal response in the glucose-tolerance test to a given dose of cortisone. I believe the difference between ACTH and cortisone in producing a diabetogenic effect in the same person is mainly a matter of how much carbohydrate-active steroid is produced by the ACTH in comparison with the dose of cortisone.

Compensations for Dietary Sacrifice

It might be worth-while to stress the theme that physicians should be extremely cautious about weight reducing programs for patients in middle life. Many of them are hardworking men and women who unfortunately receive relatively little satisfaction from their families or their jobs. These persons may be highly successful and important in their work but use intakes of various kinds to give them pleasure. If one takes away smoking, food, and alcohol from such a delicately balanced person, one has the obligation to put something constructive in its place. For two years I have seen patients who, fearing cancer, have stopped smoking. In some men this has resulted in considerable weight gains up to 40 lb. Now they dread the consequences of the added weight. This is an example of the equivalence between one set of activities and another. Depressive states with irritability are rather common in reducing programs, but mild projections are also seen. The patient may find that reading, television, or movies (visual intake) are acceptable substitutes. Other means may be found in sports, hunting, sailing, gambling, and fast motor cars. If appropriate equivalent activities are not found, the patient, his family, and his business associates are put under stress. The physician can help the patient by assisting in the correction of the unbalance and restoring a "steady state" by means of acceptable satisfactions.

From an article entitled "The Psychiatric Aspects of Obesity," by Henry W. Brosin, M.D., in *J.A.M.A.*, July 31, 1954.

The Incidence of Cholelithiasis, Cholesterosis, and Liver Disease in Diabetes Mellitus

An Autopsy Study

M. Feldman, M.D., and M. Feldman, Jr., M.D., Baltimore

It has long been known that in diabetes mellitus there is a disturbance of fat metabolism. This, and the hypercholesterolemia are held responsible for the increased tendency to cholelithiasis and gallbladder disease. On this basis there may be some relationship between diabetes and cholesterosis of the gallbladder, since in both conditions there is a disturbance of fat metabolism. To investigate this relationship we undertook the study of the findings in 1319 autopsies of adults: first to determine the incidence of diabetes, second to see how often it was associated with cholesterosis, with gallstones, and with liver disease.

In the 1319 autopsies there were 137 cases of diabetes mellitus (10.4 per cent), of which 34 were associated with gallstones and 14 with cholesterosis. In only 3 cases were both cholesterosis and gallstones present.

CHOLELITHIASIS

A review of the literature gives the impression that gallstones are more frequent in diabetic patients than in nondiabetics (table 1). The incidence in diabetics ranges from 6.0 to 33.5 per cent (average 25.1 per cent). Warren[5] reported an incidence of 31 per cent in 453 diabetic patients over thirty years, compared with 21 per cent in 500 nondiabetics. In our series of autopsies, gallstones were found in 22.7 per cent of all cases, compared with 24.8 per cent in the diabetic cases and the average incidence of 25.2 per cent recorded in the literature. There thus appears, contrary to the prevailing opinion, to be no significant difference in the incidence of gallstones among diabetic and nondiabetic patients.

From the Sinai Hospital, Baltimore, Md.

We are indebted to Dr. Tobias Weinberg, Head of the Department of Laboratories of the Sinai Hospital, for the privilege of using the autopsy material.

Address communications to Dr. Feldman at 3602 Fords Lane, Baltimore 15, Md.

CHOLESTEROSIS

So far as can be ascertained there have been no studies on the relationship between cholesterosis of the gallbladder and diabetes mellitus. In the present series, there were 165 cases of cholesterosis (12.5 per cent), including 15 cases of diabetes (9 per cent). In the 137 cases of diabetes, cholesterosis occurred in 10.2 per cent. Thus the incidence of cholesterosis of the gallbladder in the diabetic patient parallels that in the nondiabetic. Although there is a disturbance of fat metabolism in both conditions, it seems that cholesterosis is a localized condition unrelated to the fat imbalance of diabetes.

LIVER DISEASE

There has been comparatively little statistical evaluation of gross liver disease associated with diabetes. In the literature, the incidence of Laennec's cirrhosis of the liver in the general population varies from 2.4 to 18.6 per cent, depending on the source of material. According to Ratnoff and Patek[8] the incidence based on autopsy material ranges from 0.43 to 6.3 per cent. In our series there were 49 cases with Laennec's cirrhosis, and in only 3 of these was diabetes present. In the same series there were 12 cases of biliary cirrhosis, 2 of which were diabetic. Thus in the 61 cases of cirrhosis the incidence of diabetes was 8.2 per cent. Herbut and Tamaki[9] reported 12 cases of diabetes in 115 cases of cirrhosis of the liver. Comparing these percentages, one sees clearly that there is no statistical difference in the incidence of diabetes among cirrhotic and noncirrhotic patients.

In our 137 autopsied cases of diabetes there were 4 cases of cirrhosis of the liver (2.9 per cent). In the literature the incidence of cirrhosis of the liver in autopsied diabetics ranged from 2.5 to 12.7 per cent (average 7.0 per cent). From these data, it appears that cirrhosis of the liver is not commonly associated with diabetes mellitus, being merely an incidental finding.

TABLE 1
Incidence of gallstones in diabetes

	Cases of Diabetes	Cases with Gallstones	Per cent
Lieber[1]	1259	381	30.2
Seckel[2]	430	26	6.0
Jones and others[3]	68	15	22.0
Wilder[4]	197	66	33.5
Warren[5]	453	139	31.0
Joslin et al[6]	319	59	18.5
Feldman[7]	137	34	24.8
Totals	2863	720	25.1

TABLE 2
Incidence of cirrhosis of the liver in diabetes

	Autopsied Diabetics	Cirrhosis of Liver	
		No.	Per cent
Schleusner[10]	355	45	12.7
Joslin and associates[6]	319	8	2.5
Pollack and associates[11]	113	8	7.0
Feldman[7]	137	4	2.9
Totals	924	65	7.0
	Clinical Diabetics		
Joslin and associates[12]	10,235	51	0.5
Barach[13]	1,300	2	0.15
Frankel and others[14]	3,543	36	1.0
Totals	15,078	89	0.6

TABLE 3
Incidence of liver disease in diabetes

	No. of Cases
Cirrhosis	4
Hepatomegaly	4
Simple cyst (single 1, multiple 1)	2
Hemangioma	7
Adenoma (bile duct)	2
Necrosis	2
Hepatitis	1
Total	22

Other investigators have expressed similar views.

While there is little if any liver disease noted grossly in treated diabetics, there are presumed to be some physiologic or functional changes that are not obvious in gross and histological studies. Although fatty livers of varying degrees are found in untreated diabetics, this condition is uncommon in treated adult diabetics. In our 137 cases of diabetes, gross liver disease was present in 22. There appeared to be no difference in incidence between the diabetic and nondiabetic cases. It is worthy of mention that the lesions seen in the liver are for the most part unrelated to the diabetic condition. Table 3 presents the various lesions found in the 22 autopsied diabetics. These included 4 cases of cirrhosis of the liver (2 Laennec's cirrhosis, 1 biliary cirrhosis and 1 toxic cirrhosis). There were two cases with simple cysts of the liver, one single, the other multiple.

There is no unanimity of opinion regarding some of the liver abnormalities associated with diabetes mellitus. According to Duncan[15] fatty infiltration of the liver with moderate enlargement is a fairly common finding in diabetes, especially in children. According to Frankel[14] and others, most adult diabetics have little or no enlargement of the liver. According to Marble and co-workers[16] this condition in the diabetic is attributed to an excessive amount of fat and glycogen. This may be true of juvenile and untreated cases, but in the treated adult the picture differs. In our 137 cases, the majority of which had received diabetic therapy, there was gross enlargement in 4 cases indicated by the appearance and weights of 5250, 2880, 2440 and 2050 gm. respectively. In 231 diabetics Hanssen[17] found only one case of enlarged liver in patients over twenty years of age. According to Goodman[18, 19] enlargement is frequent in diabetic patients. In his clinical study it occurred in 44.5 per cent of cases. This incidence seems extremely high and is open to question because the measurements were made by percussion and palpation of the abdomen. It is not comparable to the incidence in autopsied cases.

Numerous studies have been made in diabetic patients to determine whether the liver presents any functional abnormality. Pomeranze[20] reports that 93 of 162 diabetic patients (57.2 per cent) retained over 5 per cent of bromsulphalein sodium 45 minutes after receiving a test dose of 5 mg. of bromsulphalein per kg. according to the method recommended by Mateer and associates.[21] Frankel[14] studied 319 diabetics, 46 of whom had abnormal retention; in 28 of these cases the abnormality could be attributed to causes other than diabetes, but in the other 18 the diabetes alone accounted for the abnormal retention.

SUMMARY

An autopsy study was made to determine the association of cholelithiasis, cholesterosis, and liver disease with diabetes mellitus. In 1319 adult autopsies, there were 137 cases of diabetes (10.4 per cent). The incidence of gallstones in the 127 cases was 24.8 per cent, compared

with 22.7 per cent in the whole series and an average of 25.2 per cent in the literature. It is concluded that gallstones are no more prevalent in diabetics than in nondiabetics.

Cholesterosis of the gallbladder was present in 14 of the 137 diabetics (10.2 per cent). The incidence of cholesterosis in the 1319 autopsies was 12.5 per cent, and that in the diabetics was 10.2 per cent.

Laennec's cirrhosis of the liver occurred in only 4 of the 137 diabetic cases (2.9 per cent). The autopsy study revealed no gross liver disease in the diabetics, although others have reported abnormal liver function in diabetic patients.

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ABSTRACTS

Allegretti, Niksa, and Vukadinovic, Gjorgje (*Inst. of Physiology, The Medical Faculty, Univ. of Zagreb, Zagreb, Yugoslavia*): EFFECT OF ASCORBIC ACID ON INSULIN SENSITIVITY IN THE RAT. Am. J. Physiol. *177*: 264-68, May 1954.

The authors report a study of ascorbic acid action on carbohydrate metabolism and insulin sensitivity. Ascorbic acid administered to intact, normal and demedullated rats produced no significant changes in the blood sugar level; that is, it had no influence on the activity of endogenous insulin. The injection of ascorbic acid into normal and demedullated rats previously given insulin resulted in a greater degree of hypoglycemia, indicating greater sensitivity to insulin, and more died in convulsions.

The authors hypothecate that ascorbic acid suppresses the secretion of C-11 oxygenated corticoids by shifting the cortical secretion toward corticoids which regulate electrolyte metabolism.

Attygalle, Nicholas; and Jayasekera, B. P. N. (*Dept. of Obstetrics and Gynecology, Univ. of Ceylon*): DIABETES AND PREGNANCY. Ceylon M. J. 2:8-15, April 1953.

The literature on diabetes complicating pregnancy is reviewed. The effect of large doses of stilbestrol on the glucose tolerance curve is presented in two cases. An appreciable fall in blood sugar level was noted.

Bacon, Melvin (*Sanford, Me.*): A TOWN OBSERVES NATIONAL DIABETES WEEK. J. Maine M. A. *45*:119:21, May 1954.

This paper describes a plan whereby a town may carry out a diabetes program during National Diabetes Week. The various activities of Diabetes Week and the response to these activities indicate the value of such an endeavor in educating the public concerning diabetes. There was a gratifying response from the public indicating an interest in learning about diabetes. Of 247 school children tested 3.6 per cent showed glycosuria. Of 572 adults tested, there were 1.2 per cent known cases of diabetes in addition to 2 per cent newly discovered cases of glycosuria. The cases with glycosuria were referred to their family physicians for further evaluation.

Benton, Paul C. (*Tulsa, Okla.*): THE EMOTIONAL ASPECTS OF DIABETES MELLITUS. J. Oklahoma M. A. *46*:295-300, November 1953.

The onset and course of diabetes mellitus may be altered by the emotional state of the individual. The emotional factors require evaluation in the treatment of the disease. The proper psychological emphasis may spell the difference between the successful or unsuccessful management of the disease. One must treat the individual as well as his diabetes.

Berger, Hermann: HYPERINSULINISM. ITS DEFINITION, DIAGNOSIS, AND TREATMENT. Der Chirurg. *23*:552, 1952. Abstr. from Surg. Gynec. & Obst. *97*:257, Sept. 1953.

The author believes that the blood sugar curve can indicate the basis of hypoglycemia, and thus offer a guide to conservative or operative management. Curves are depicted for organic hyperinsulinism, functional hyperinsulinism, hepatogenous hypoglycemia, and other types.

Blotner, Harry (*Boston, Mass.*): ATTEMPTED SUICIDE WITH INSULIN. Am. J. M. Sc. *227*:387-90, April 1954.

The author reviews the 8 reported cases in the literature of attempted suicide with insulin, of which 5 recovered and 3 died. The patients who recovered took doses ranging from 20 to 400 units of regular insulin and from 490 to 2,000 units of protamine insulin; the latter dose exerted a severe hypoglycemic effect for 6 days. In the 3 fatal cases, the insulin dosage was 400 units and 2,400 units of regular insulin in two and was unknown in the third. Post-mortem examinations revealed cerebral edema and intracranial hemorrhage.

The author reports the only recorded attempt at suicide with insulin in a nondiabetic. A 46-year-old physician took 200 units of regular insulin; he also took 2¼ grains of morphine and 9/20 grain of dilaudid. He readily recovered under therapy with glucose given intravenously, caffeine and nalline.

Committee on Foods, Drugs, Cosmetics and Devices (*New Haven, Conn.*): A NEW INSULIN. Connecticut M.J. *18*:390, April 1954.

Dr. Greenhouse stated that a new type of insulin (Insulin Lente Type 70/30) had recently been offered for clinical investigation. This insulin contains 0.2 mg. of zinc per 100 units, and also contains an acetate buffer. It dissolves slowly at the *p*H of the blood; no foreign protein is present. Preliminary clinical results indicate that it is an intermediate-acting insulin. It has a slightly longer action in some patients.

Cram, Robert H. (*Univ. of Pennsylvania Hosp., Philadelphia, Pa.*): DIABETIC ARTHROPATHY. S. Clin. North America *33*:1759-63, December 1953.

The author briefly reviews diabetic arthropathy and presents two illustrative cases.

Daughaday, W. H.; and Weichselbaum, T. E. (*Depts. of Med. and Surg., Washington Univ. Sch. of Med. and Barnes Hosp., St. Louis, Mo.*): UTILIZATION OF INTRAVENOUS FRUCTOSE IN DIABETIC ACIDOSIS AND IN A PANCREATECTOMIZED HUMAN. Metabolism 2: 459-67, September 1953.

Fructose administered intravenously to nine patients with severe diabetic acidosis, receiving insulin, was removed promptly from the blood stream with little rise in total blood sugar except when the rate of infusion was greater than 1.9 gm. per kg. per hour. The carbohydrate retention varied from 35 to 95 per cent (mean —72.5) of the administered fructose, depending on the rate of infusion. When administered to a pancreatectomized woman with mild ketonuria, fructose was also promptly removed from the blood. In the absence of insulin, however, there was a corresponding increase in blood glucose, presumably due to the conversion of fructose to glucose. This latter effect could be abolished with three units of insulin. These results suggest that the therapeutic use of intravenous fructose in diabetic acidosis would result in less hyperglycemia and glycosuria than glucose.

Davis, T. R. A.; and Mayer, J. (*Dept. of Nutrition, Harvard School of Public Health, Boston, Mass.*): IMPERFECT HOMEOTHERMIA IN THE HEREDITARY OBESE-HYPERGLYCEMIC SYNDROME OF MICE. Am. J. Physiol. *177*:222-26, May 1954.

Study of the extreme sensitivity to cold leading to death of obese-hyperglycemic mice on exposure to temperatures normally endured by non-obese siblings reveals that the fundamental defect in the former is their inability to raise their metabolic rate in response to cold. Oxygen consumption which is normally doubled in thin animals under the experimental conditions is not increased in the obese animals. Obesity per se, decreased thickness of peloge, failure of shivering and pilo-erection and decrease in spontaneous exercise were eliminated as causative factors in the failure of thermogenesis.

DeHoff, John B.; and Ozazewski, John (*Depts. of Med. and Ophthalmology, Univ. of Md. Med. Sch. Baltimore, Md.*): ALPHA TOCOPHEROL TO TREAT DIABETIC RETINOPATHY. Am. J. Ophth. *37*:581-82, April 1954.

The empirical use of alpha tocopherol acetate, in dosage from 300 mg. to 600 mg. every day for protracted periods, had no demonstrable effect on the progression of diabetic retinopathy, as observed in 12 patients.

Ditzel, Jörn (*Baker Clin. Res. Lab., New England Deaconess Hosp., and the Joslin Clin., Boston, Mass.*): MORPHOLOGIC AND HEMODYNAMIC CHANGES IN THE SMALLER BLOOD VESSELS IN DIABETES MELLITUS. New England J. Med. *250*:541-46, April 1, 1954.

The capillary changes in diabetes are widespread, occur principally in the venous part, and appear to have a common pathology characterized principally by hyalinization. The relation between the metabolic disturbance and the vascular degeneration is unknown.

Since the capillaries show the first and probably the purest form of any vascular abnormality and since it appears that the smaller blood vessels and arterial blood flow in the bulbar conjunctiva are at least representative of the subcutaneous vascular system and its hemodynamics, further investigation of the problem of vascular degeneration may be properly approached through the study of the conjunctival vessels. Such a long-term project has been started, and a preliminary report will be presented in a paper to be published later.

Drury, Douglas R. and Wick, Arne N. (*Scripps Metabolic Clinic, La Jolla, and the Dept. of Physiology, Sch. of Medicine, Univ. of Southern California, Los Angeles, Calif.*): METABOLISM OF MANNOSE BY THE EXTRAHEPATIC TISSUES. Am. J. Physiol. *177*:535-38, June 1954.

Mannose, like glucose and galactose, will pass from the extracellular to the intracellular compartment of the extrahepatic tissues. Insulin accelerates the rate of this transfer. Glucose and mannose compete to enter into the reaction accelerated by insulin; that is, glucose reduces the rate at which mannose is transferred into the cells under insulin action.

In the eviscerated non-nephrectomized rabbit, mannose injected into the blood is largely excreted by the kidney. This observation is used to prove that little if any circulating mannose is changed to glucose by this preparation.

The extrahepatic tissues under insulin action oxidize considerable amounts of mannose to carbon dioxide.

DuBois, Kenneth P.; Deroin, Jere; and Cochran, Kenneth W. (*U.S. Air Force Radiation Laboratory and the Dept. of Pharmacology, Univ. of Chicago*): INFLUENCE OF NITROGEN MUSTARDS ON CITRIC ACID SYNTHESIS IN VIVO. Proc. Soc. Exper. Biol. & Med. *81*:230-34, October 1952.

The influence of nitrogen mustards on citrate synthesis in rat tissues *in vivo* was studied using the fluoroacetate technic of Potter. The results of this study demonstrated that HN 1 and HN 2 produce alterations in citrate synthesis in certain tissues which are qualitatively similar to those produced by X ray. Thus, a decrease in citrate synthesis was observed in the spleen and thymus gland of nitrogen mustard-poisoned animals, and a marked increase in citrate accumulation was observed in the liver of male rats. The increase in citrate accumulation in the liver was evident after doses far below the LD_{50} and persisted for several weeks following sublethal doses of the nitrogen mustards.

Duperie, R.; Dubarry, J. J.; Mayer, G.; Couteau, Mlle.: A CASE OF MALIGNANT INSULINOMA. Arch. mal. app. digest. *41*:882, 1952. Abstr. from Surg. Gynec. & Obst. *97*:258, September 1953.

The authors report on a case of malignant insulinoma in a woman 54 years of age. There were numerous metastatic lesions in the liver and in the lymph nodes along the splenic artery.

Editorial: THE DIABETOGENIC ACTIVITY OF PITUITARY EXTRACTS. Nutrition Rev. *11*:315-17, October 1953.

The conclusion from the papers reviewed supports the view that diabetogenic activity is intrinsic in the growth hormone molecule and the separation of diabetogenic and growth activity claimed by Raben and Westermeyer has not been confirmed by Reid.

Editorials and Comments (*Chicago, Ill.*): EMPLOYMENT FOR DIABETICS. J.A.M.A. *154*:1005, March 20, 1954.

This editorial based on the report of the Committee on Employment of the American Diabetes Association emphasized its philosophy that a controlled diabetic is a good employment risk, and that by virtue of his capability of performing a full day's work satisfactorily despite his disease, the diabetic should not be classed with the physically handicapped. During the past five years, the Association, through its committee on employment, has endeavored to reach some unanimity of opinion in the formulation of recommendations to labor and management regarding the industrial utilization of the diabetic. With these employment standards in realistic usage by employers and personnel directors, the diabetic applicant should be considered just as eligible for work as the nondiabetic candidate. His effective contribution to industry has been demonstrated, and with continuing cooperative efforts among labor, employers, and professional groups toward hiring the diabetic, employment prejudice will continue to abate.

Editorials and Comments (*Chicago, Ill.*): TRAUMA AND DIABETES. J.A.M.A. *154*:1182, April 3, 1954.

The thesis that sudden trauma can cause diabetes has steadily lost support with the expanding knowledge of the nature of the disorder. However, evidence has accumulated to show that trauma indirectly can activate, or accelerate, the appearance of latent diabetes in the hereditarily predisposed, particularly if accompanied by infection, reduced muscular exercise, overweight, overeating, disease of the pituitary, thyroid, adrenal, or liver, and pregnancy.

Trauma, as the cause of diabetes, should be distinguished from the discovery of diabetes after an accident. Physical injury to the pancreas is recognized as a cause of diabetes, although there are only very few fairly well authenticated cases in the literature. Physical and psychological trauma cannot be advanced as a cause of diabetes. It is universally recognized that an accident may temporarily activate diabetes, but, when the results of the trauma are relieved, the diabetes reverts to its previous status.

Edwards, Edward A. (*Peter Bent Brigham Hosp. and Harvard Med. Sch., Boston, Mass.*): NATURE AND MANAGEMENT OF LIMB PROBLEMS IN THE DIABETIC. Rhode Island M. J. 36:711-15, December 1953.

With progressive increase in our medical and surgical armamentarium, we should be even more watchful for preventable and treatable limb complications of diabetes. Lack of diabetic control, preventable infection, and unheeded neuritis are still responsible for much morbidity and loss of limbs. Teaching the patient control of his diabetes and hygiene of his limbs cannot be looked upon as having been accomplished at the time of discovery of the diabetes. It has to be a repetitive activity. Moreover, the doctor must share actively in the process of hygiene by discovering and treating early the complications of the disease.

Ershoff, B. H.; Geiger, E.; Bittner, E.; and Graham, T. (*Emory W. Thurston Lab., Los Angeles, and the Institute of Nutritional Research, Los Angeles, Calif.*): COMPARATIVE EFFECTS OF GLUCOSE, FRUCTOSE AND SUCROSE ON THE THIAMINE REQUIREMENT OF THE RAT. Exper. Med. & Surg. 11:293-96, 1953.

Immature female rats were fed thiamine-deficient diets containing either glucose, fructose, or sucrose as the source of dietary carbohydrate. No significant differences in gross appearance, rate of depletion, or length of survival were noted among rats fed the various diets.

Fodden, John H.; and Read, Willard O. (*Univ. of South Dakota Med. Sch., Vermillion, So. Dak.*): THE ACTIVITY OF EXTRACTED PANCREATIC HYPERGLYCEMIC-GLYCOGENOLYTIC FACTOR AFTER COBALTOUS CHLORIDE AND SYNTHALIN A. Endocrinology 54:303-10, March 1954.

From the literature, it is noted that cobaltous chloride in the intact animal appears to cause extreme degeneration of the alpha cells yet has little or no effect upon the blood sugar of such an animal, while synthalin A produces an inconstant hydropic vacuolation and degranulation of some alpha cells associated with profound hypoglycemia.

The authors found that in rabbits, synthalin A given intravenously seemed to completely inhibit the hyperglycemic-glycogenolytic function of the islet tissue, leaving the insulin potency undisturbed or even enhanced. Used in conjunction with alloxan, the resultant pancreatic extract has an action similar to a phosphate-chloride buffer solution.

Intravenous cobaltous chloride, despite the pathologic picture of alpha cell swelling, edema, and vacuolation, does not cause functional incapacity, and it is suggested that it prevents the release of hyperglycemic-glycogenolytic factor with subsequent intracellular accumulation as was found to be the case on extraction of such treated pancreases.

Foreign Letters (*London, Gt. Brit.*): FIELD WORK OF A DIABETIC CLINIC. J.A.M.A. 153:1038, November 14, 1953.

There is a need for field work in the care and after-care of the diabetic patient. Teaching the diabetic has to be slow, painstaking, and above all consistent. It is not always possible to have consistency in treatment with different schools of thought, neither of which are wrong but which are confusing to the patient.

Foreign Letters (*London*): GENERAL PRACTITIONERS' RECORDS. J.A.M.A. 153:1469, December 19, 1953.

A recently published report on the records of general practitioners was used as a source of general morbidity statistics and to study the problems associated with this use of these records. Altogether, 27,365 patients were included in the survey. For diabetes, there was a patient-consultation rate of 3.4 per 1,000 practice population.

Forrest, Andrew P. M., and Code, Charles F. (*Section of Physiology, Mayo Clinic and Mayo Foundation,*

Rochester, Minn.): EFFECT OF SYMPATHECTOMY AND VAGOTOMY ON THE INHIBITION BY INSULIN OF HISTAMINE-INDUCED SECRETION IN SEPARATED (HEIDENHAIN) CANINE POUCHES. *Am. J. Physiol.* 177:430-32, June 1954.

The inhibitory effect of insulin on histamine-induced gastric secretion was confirmed in dogs which had separated gastric pouches. The role of the nerve supply to the gastric mucosa in the production of this inhibition was studied by tests utilizing pouches in various stages of denervation. The conclusion was reached that the inhibition of histamine-induced gastric secretion by insulin is not dependent on the vagal or sympathetic nerve supply to the stomach but is related to the decreased concentration of sugar in the blood caused by the administration of insulin in a dose of 1 to 2 units per kg. intravenously.

Fox, J. G.; McConnell, R. B.; Pemberton, H. S.; and Watson, D. C. (*Diabetic Clin., David Lewis Northern Hosp.*): METHOD OF PREVENTING INSULIN ATROPHY. Brit. M. J. 2:1202-03, November 28, 1953.

It would seem that the addition of hyaluronidase to soluble insulin has prevented atrophy developing, whereas, with insulin alone, atrophy had appeared in a few months. The chief benefit from the use of this method, if its value is confirmed, would appear to lie in the alleviation of this unsightly effect of insulin therapy, which so commonly occurs in children and young women. There are some practical points for consideration before the method can be applied to the routine outpatient treatment of diabetics. At present it is believed that the insulin-hyaluronidase mixture must be freshly prepared each day, as its spreading action begins to diminish after eight hours. A more stable preparation would have obvious advantages.

Gandevia, Bryan (*Royal Melbourne Hosp., Melbourne, Australia*): THE ASSOCIATION BETWEEN HYPOGLYCAEMIA AND MYOCARDIAL INFARCTION. Medical Journal of Australia 1:33-36, January 9, 1954.

In a consecutive series of 50 cases of recent myocardial infarction proved at autopsy, six subjects were found to have had an antecedent hypoglycemic episode at approximately the time of onset of the infarct. In a series of 55 diabetic patients who came to autopsy, the incidence of antecedent hypoglycemia was found to be significantly higher in those who had died from myocardial infarctions than in those who had died from other causes. The literature is summarized, and the conclusion is reached that hypoglycemia, probably acting indirectly by producing an increase in cardiac work, may be a factor in the production of myocardial infarction, angina pectoris, and some cases of cardiac neurosis.

Gelfand, Maxwell L. (*New York*): TREATMENT OF HERPES ZOSTER WITH CORTISONE. J.A.M.A. 154:911-12, March 13, 1954.

A brief course of cortisone therapy was reported to be useful in the treatment of severe and extensive herpes zoster, since it appeared to shorten the acute phase, diminish the intense pain, and reduce the incidence of complications. It should be reserved for patients in the older age group and those failing to respond to the conventional methods. Despite the extensive and severe involvement, all patients felt so well that they were able to continue their usual work. None of the usual signs of undesirable metabolic or physiological disturbances, such as a gain in weight, glycosuria, alkalosis (as measured by the carbon dioxide content of the blood), or hypopotassemia (as seen in the electrocardiogram), was present.

Goldner, Martin G.; Volk, Bruno W.; and Lazarus, Sydney S. (*Jewish Sanitarium and Hosp. for Chronic Diseases, Brooklyn, N. Y.*): EFFECT OF ALPHA-CELL DESTRUCTION ON THE HGF CONTENT OF THE CANINE PANCREAS. J. Clin. Endocrinol. & Metab. 14:184-92, February 1954.

Extracts from normal and alloxanized pancreas when injected intravenously into fasting rabbits or dogs cause a significant transitory hyperglycemia. Similar results have been obtained after the injection of extracts from pancreas in which the alpha cells have been severely damaged or destroyed by the prior administration of cobalt. These results seem to suggest that the hyperglycemic-glycogenolytic factor is not produced by the alpha cells but elsewhere in the pancreas.

Goodman, Joseph I.: REVIEW: INSULIN (HYPOGLYCEMIC) REACTIONS IN DIABETIC PATIENTS. Metabo-

lism 2:485-99, November 1953.

A discussion of the etiology, physiology, and pathology of insulin-induced hypoglycemia is presented.

Goodman, Joseph I.; and Goldberg, Leonard B. (*Mt. Sinai Hosp., Cleveland, Ohio*): DIABETES MELLITUS IN THE AGED. Ohio Med. J. *49*:981-85, November 1953.

Fifty-nine diabetic patients whose diabetes was first discovered after the age of 60 are described. The findings in general correspond to those previously pictured in standard texts.

Goodyer, Allan V. N.; Welt, Louis G.; Darragh, James H.; Abele, William A.; Meroney, William H. (*Dept. of Internal Medicine, Yale Univ. School of Medicine, New Haven, Conn.*): EFFECT OF GLUCOSE DIURESIS ON RENAL EXCRETION OF BICARBONATE: Proc. Soc. Exper. Biol. & Med. *86*:19-22, May 1954.

Sodium bicarbonate was injected intravenously into three normal males at rates that resulted in bicarbonate making up a large proportion of the urinary anion excretion. Hypertonic glucose infusions were then superimposed producing an osmotic glucose diuresis. Under these conditions the rate of excretion of bicarbonate decreased, while the rates of excretion of other electrolytes (Na, K, Cl) increased. The authors suggest that the slight increase in the serum pCO_2 observed might be the factor tending to increase the net tubular reabsorption of bicarbonate.

Gounelle, Hugues; Marnay, Christiane; and Rabii, Hasan. (*Paris, France*): HYPOGLYCEMIA-INDUCING ACTION OF VITAMIN E IN THE NORMAL AND DIABETIC SUBJECT. La Presse Médicale *62*:888-90, June 9, 1954.

In the diabetic subject, tocopherol does diminish the fasting glycemia and likewise the glycemia curve following injection of "retard" insulin. Experimental alloxan diabetes in rabbits is also ameliorated by oral administration of tocopherol.

Green, Robert C., Jr. (*Winchester, Va.*): THE DIAGNOSIS AND TREATMENT OF GLYCOSURIA. Virginia M. Month. *80*:658-64, December 1953.

A diagnosis of diabetes mellitus can usually be made without hesitation or reservation. On the other hand, when there is persistent gross glycosuria and markedly abnormal values for blood sugar whether or not symptoms are present, cases of glycosuria with normal or borderline blood sugar values may present real diagnostic problems. Any patient who has glycosuria should be suspected of having diabetes until its presence is disproved. Since the label "diabetic" often carries serious psychologic and financial penalties for the patient, the physician should make every effort to establish a correct diagnosis.

Greenhouse, Barnett (*New Haven, Conn.*): NPH INSULIN: ITS USE IN GENERAL PRACTICE. M. Times *80*:706-08, November 1952.

The author reviews the use of NPH insulin in general practice and points out that all insulins have a place in the treatment of diabetes. Certainly in the smaller dosages, any of the available insulins will do as well. In the large majority of patients, NPH insulin will give adequate control; but in the severer cases, admixture with crystalline zinc insulin in the same syringe is necessary. Unlike protamine zinc insulin, however, NPH insulin does not combine with the added crystalline insulin, which remains practically free to act as if given by separate injection. This serves to sharpen and accelerate the effect of NPH insulin, and if enough crystalline insulin is used "to tuck away the breakfast," less NPH insulin will be needed, with less chance for overdosage.

Gysin, W. M.; and Wilson, J. L. (*Dept. of Psychiatry & Neurology, Veteran's Administration Hosp., Omaha, Neb.*): HYALURONIDASE IN INSULIN COMA THERAPY. Dis. Nerv. System *15*:138-41, May 1954.

Hyaluronidase (50 to 75 TRU of Wydase) was used with insulin and it was found that: (1) Induction of coma was smoother and more rapid. (2) Little time change in onset of coma compared to insulin without hyaluronidase. (3) 35 to 40 per cent less insulin needed to produce same effect. (4) Delayed adverse reactions were lessened by up to 73 per cent.

Hackedorn, Howard M.; Crampton, Joseph H.; and Palmer, Lester J. (*Univ. of Washington and the Mason Clin., Seattle, Wash.*): INTRAVENOUS GLUCOSE TOLERANCE TEST IN LIVER DISEASE AND DIABETES MELLITUS. Northwest Med. 53:257-62, March 1954.

The intravenous glucose tolerance test was performed in six normal young adults and in twenty patients with abnormal carbohydrate metabolism whose disorder without the test was not clearly recognized. The authors believed that the use of the intravenous glucose tolerance test together with liver function studies enabled them to separate disorders of carbohydrate metabolism due to liver disease from diabetes mellitus in fifteen cases. In five cases both diseases were present. After intravenous administration of glucose, the rate of glucose fixation was reflected by the fall of serum inorganic phosphorus. There is a relatively small drop in diabetic patients. There is a moderate drop in patients with liver disease. Patients with both diabetes and liver disease showed a slight fall of serum inorganic phosphorus, which is within normal range, and, in addition, showed excessive glycosuria.

Hall, James C. (*Newark College of Arts & Sciences, Rutgers Univ., Newark, N. J.*): THE EFFECT OF INSULIN ON THE OXYGEN CONSUMPTION OF MAMMALIAN MUSCLE. Science *119*:813-14, June 4, 1954.

The author reports upon the oxygen consumption of strips of normal and diabetic rabbit muscle, noted no significant difference between the oxygen consumption of the two types, but observed a different effect of insulin in the normal and diabetic muscle. While the addition of citrate stimulated the oxygen consumption by over 60 per cent in both types, insulin had no significant effect in the normal but increased the oxygen O_2 uptake by an additional 60 per cent in the diabetic. The author's data indicate a definite difference in the response of normal and diabetic rabbit muscle to insulin.

Herbain, M. Maurice: EXPERIMENTAL IDENTITY OF THE RETARDING EFFECT OF CLUPEINE-ZINC INSULIN AND SALAMINE-ZINC INSULIN PREPARATIONS. Annales Pharmaceutiques Françaises *12*:121-25, February 1954.

The author made a chemical comparison of the effects of insulin modified by protamine from two fish sources, salmon and herring. He found there was no difference in the two preparations.

Hewitt, John E.; Hayes, Thomas L.; Gofman, John W.; Jones, Hardin B.; and Pierce, Frank T. (*Donner Lab. of Med. Physics, the Radiation Lab., Dept. of Physics, Univ. of California, Berkeley, Calif.*): EFFECTS OF TOTAL BODY IRRADIATION UPON LIPOPROTEIN METABOLISM. Am. J. Physiol. *172*:579-87, March 1953.

The authors report an excellent correlation between the high level of total lipoprotein 30 hours after irradiation and the subsequent death of the animal. A serum opalescence is associated with low-density lipoprotein only, not with total lipoprotein level. Changes in the lipoprotein levels after irradiation are consistent with the theory of conversion of low-density lipoprotein to higher density components. The injection of toluidine blue produces changes in the lipoprotein pattern similar to those shown after irradiation.

Holcomb, Blair; Page, Otto C.; and Stephens, John W. (*Portland, Ore.*): LENTE INSULIN: CLINIC STUDY OF A NEW INSULIN ZINC PREPARATION OF PROLONGED ACTION. Northwest Med. *53*:239-41, March 1954.

The authors report their experiences with fourteen ambulatory patients who had diabetes previously controlled on NPH insulin alone, or mixtures of NPH and regular insulin, and who were treated with lente insulin or a mixture of lente and regular insulin. The control with lente insulin alone compared favorably with that obtained with NPH insulin alone. The authors found that the duration of action of lente insulin did not seem to be greatly affected when mixed with regular insulin, but that the regular insulin did not act as rapidly or as potently when added to lente insulin.

Hurwitz, David; and Runyan, John W., Jr. (*Diabetes Serv., Boston City Hosp., Diabetes Sect., U. S. Public Health Serv.*): MANAGEMENT OF THE AMBULATORY DIABETIC PATIENT. New England J. Med. *250*:361-65, March 4, 1954.

An outline for the management of the diabetic patient in the clinic or office on an ambulatory basis is presented.

Hutchinson, William B. (*Seattle, Wash.*): PRESENT STATUS OF CARCINOMA OF THE PANCREAS. A.M.A. Arch. Surg. *68*:62-68, January 1951.

An analysis of the treatment of carcinoma of the pancreas

at the Swedish Hospital from 1947 through 1952 and those currently reported series in the literature makes us cognizant immediately of the disappointment and errors in judgment that occur. There is little evidence to show that we alter the natural history of carcinoma of the pancreas with surgery, and with rare exceptions this is a fatal disease. Radical resection for carcinoma of the pancreas should be undertaken in those patients in whom the carcinomatous process is limited strictly to the confines of the pancreas or the immediately adjacent duodenum. This will therefore include ampullary, lower bile duct, and duodenal carcinomas, which are favorable lesions for resection. In patients in whom the carcinoma has extended beyond the strict confines of the pancreas, a well selected palliative procedure should be done when indicated.

Jackson, W. P. U. (*Depts. of Med., Univ. of Capetown, South Africa, and Mass. Genl. Hosp., Boston, Mass.*): THE PREDIABETIC SYNDROME. LARGE BABIES AND THE (PRE)DIABETIC FATHER; PREDIABETIC AND (PRE) ACROMEGALIC WOMEN. J. Clin. Endocrinol. & Metab. *14*:177-83, February 1954.

Women in whom overt diabetes develops in later life are apt to produce large babies and stillbirths. In the series presented in this report, over 60 per cent of such women claimed babies who weighed more than 10 pounds at birth. At present, the most favored explanation attributes this phenomenon to an excess of circulating growth hormone. There is little evidence for this hypothesis, and much against it. Acromegalics, for instance (in a small personal series), do not appear to have a great tendency to produce babies of excessive size. New evidence is presented concerning the children of diabetic fathers which indicates that the birth weights of such children are above average, whereas the stillbirth rate is not increased. These data suggest that the onus of production of large babies cannot be borne entirely by maternal factors but must in part be an inherited phenomenon, linked in some way to the diabetic genetic constitution of either parent. The concept of the "prediabetic" father is thus born.

Janes, Ralph G.; and Winnick, Theodore (*Dept. of Anat. and the Radiation Res. Laboratory, State Univ. of Iowa, Coll. of Med., Iowa City*): DISTRIBUTION OF C^{14}-LABELED ALLOXAN IN THE TISSUES OF THE RAT AND ITS MODE OF ELIMINATION. Proc. Soc. Exper. Biol. & Med. *81*:226-29, October 1952.

Two alloxan preparations, labeled in the 2 and 5-position with C^{14}, were administered subcutaneously to rats. Both labeled compounds were rapidly excreted in the urine, to the extent of 90-95 per cent in 22 hrs. Negligible proportions of the C^{14} were found in urea. With either tracer or diabetogenic doses, the radioactivity was highest in the kidneys and plasma and reached a peak at approximately 15 mins. The other tissues studied, including pancreas, had much lower C^{14} concentrations. With either alloxan 2 or 5-C^{14}, very little radioactivity appeared as $C^{14}O_2$ in expired air. It is concluded that the alloxan molecule does not undergo extensive catabolism in the rat.

Jokipii, S. G. (*First Med. Clin. Univ. of Helsinki*): LATE COMPLICATIONS OF DIABETES. Ann. med. int. Fenniae *42*:185-98, 1953.

The purpose of the study was to determine the incidence of late complications of diabetes among Finnish patients, with special attention to other diseases simultaneously affecting the diabetics. The series comprised 119 autopsies of diabetic patients and 384 patients treated in various hospitals. Retinopathy was diagnosed in 18.7 per cent, nephropathy, excluding transitory and extrarenal albuminuria, in 12.7 per cent, albuminuria in 36.0 per cent of unselected cases, polyneuritis in 2.8 per cent and leg gangrene in 5.5 per cent. The complications were rare if the patient had suffered from diabetes for less than 8 years. Their frequency increased with the duration of the disease. Hypertension occurred in 51.0 per cent of the cases of diabetes. Among the autopsied cases, active tuberculosis was present in 13.4 per cent, 3 times more often in men than in women, and cholelithiasis in 18.5 per cent, of whom ¾ were women. There were 4 cases of cancer of the pancreas and 14 other malignant tumors among the 119 autopsy cases.

Jokipii, S. G., and Turpeinen, Osmo (*Dept. of Med. Helsinki Univ., Helsinki, Finland*): KINETICS OF ELIMINATION OF GLUCOSE FROM THE BLOOD DURING AND AFTER A CONTINUOUS INTRAVENOUS INJECTION. J. Clin. Investigation *33*:452-58, March 1954.

Glucose solutions were injected intravenously at a constant relatively slow rate during a period of 60 minutes into human subjects. The blood glucose level was determined in samples of capillary blood during and, in

part of the experiments, also after the injection.

The experimental results were in good agreement with the hypothesis that the elimination of the exogenous glucose from the blood takes place at the rate of a first-order reaction. The form of the blood glucose-time curve is determined by, besides the rate of injection, two characteristics of the subject: k, the specific reaction-rate constant or the velocity constant of elimination, and v, the apparent initial volume of distribution.

Kempner, Walter (*Dept. of Med., Duke Univ. Sch. of Med., Durham, N. C.*): RADICAL DIETARY TREATMENT OF HYPERTENSIVE AND ARTERIOSCLEROTIC VASCULAR DISEASE, HEART AND KIDNEY DISEASE, AND VASCULAR RETINOPATHY. GP 9:71-92, March 1954.

Patients with diabetes mellitus not only tolerate the rice diet well, but also, in a significant number of patients, the blood sugar level and the insulin requirement are lowered. The diet may also have a special value in the treatment of many patients with diabetes mellitus because of the dangerous role played by hypercholesterolemia in this disease. Forty-eight patients with diabetes mellitus and complicating renal or vascular disease were treated with the rice diet. The period of observation was from eight weeks to almost six years (average fifty-nine weeks). In 17 of the 48 cases, there was a change of more than 30 mg. in the fasting blood sugar level; in 3 of them the fasting blood sugar level increased; in 14 it decreased. The others either had marked fluctuation in blood sugar level or showed only minor changes. The favorable response of these patients and the fact that a great number of diabetics die of vascular disease or at least are incapacitated by it suggest that the rice diet should be used in the treatment of diabetics who are beginning to show cardiac, retinal, renal, or peripheral vascular disease.

Kinney, Janet R. (*Dept. of Med., Univ. of Illinois, Chicago, Ill.*): WEIGHT REDUCTION IN AN OBESE DIABETIC. Ann. Int. Med. 40:1024-26, May 1954.

The case presented illustrates the importance of the control of the mechanism of overeating in the dietary management of the obese diabetic. The beneficial effect of weight reduction on insulin requirement is illustrated. The importance of listening to as well as instructing the patient is emphasized.

Kinsell, L. W.; Michaels, G. D.; Margen, S.; Partridge, J. W.; Boling, L.; and Balch, H. E. (*Inst. for Metabolic Res., Highland Alameda Ct. Hosp., Oakland, Calif.*): THE CASE FOR CORTICAL STEROID HORMONE ACCELERATION OF NEOGLUCOGENESIS FROM FAT IN DIABETIC SUBJECTS. A SUMMARY OF FIVE YEARS' INVESTIGATIVE WORK. J. Clin. Endocrinol. & Metab. 14:161-76, February 1954.

Studies carried out in the authors' laboratory in a period of nearly five years are compatible with the concept that cortical steroids accelerate the formation of carbohydrate from fat. They indicate further that prevention of depletion of potassium, and possibly of sodium, may be of importance in preventing steroid hormone-induced insulin resistance.

Kleinsorge, Hellmuth; and Schuchardt, Hanns (*Medizinischen Universitats—Poliklinik Jena*): THE INFLUENCE OF AN ATP COMPLEX COMPOUND ON BLOOD SUGAR. München. med. Wchnschr. 96:227-29, February 26, 1954.

According to past investigations and experiences the adenosinetriphosphoric acid complex administered orally acts as a phosphate donor, stimulates the activity of the hexokinase, and increases the glycogen in the liver while acting as a liver protecting substance.

Komrower, George M. (*St. Mary's Hosps., Manchester, and the Dept. of Child Health of the Univ. of Manchester*): BLOOD SUGAR LEVELS IN BABIES BORN OF DIABETIC MOTHERS. Arch. Dis. Childhood 29:28-33, February 1954.

Estimations of the blood sugar level during the first 24 hours of life were made on 21 normal infants and 40 infants born of diabetic mothers. Twenty-five of the latter 40 babies were given 50 per cent glucose in the first eight hours of life. The normal infants showed a wide scatter of blood sugar levels, but there was no dramatic rise or fall in the figures in any one case. The babies of diabetic mothers revealed a rapid drop in the first hours of life with a slow rise towards the end of the first 24 hours. There were considerable variations in the figures obtained. The administration of a 50 per cent oral glucose solution did not make any appreciable difference to the blood sugar levels obtained compared with the group of infants to whom glucose was denied. The clinical picture of hypoglycemia in infancy is described, and the fact that it is an uncom-

mon finding is stressed. It is suggested that few, if any, babies born of diabetic mothers die as the result of hypoglycemia.

Kossmann, F.; and Pirrung, E. (*Germany*): OBESITY AS DIENCEPHALOHYPOPHYSIAL DYSREGULATION. Die Medizinische, Stuttgart, 27/28:897, July 11, 1953. (Abstr. from J.A.M.A. *153*:1127, November 21, 1953.)

The authors believe that obesity in women between the second and fourth decade of life is caused endogenously by diencephalohypophysial dysfunction, and exogenous factors, such as polyphagia, play a secondary part only. This concept was supported by the results of the Staub-Traugott test which revealed pathological changes in the sense of a negative effect in 20 cases with a repeated elevation of the blood sugar level by 40 to 100 mg. per 100 cc. after the second oral dose of dextrose. The weight of the anterior lobe of the pituitary is greater in women than in men; this, as well as the fact that the weight of the anterior lobe of the pituitary increases by 20 per cent during pregnancy, may explain the predisposition of women to obesity.

Kurschner, David M.; Eisenoff, Henry; Gitlow, Samuel (*New York, N. Y.*): THE ROLE OF DIET AND INSULIN IN DIABETES MELLITUS. Am. Pract. & Digest Treat. 5:497-504, July 1954.

An excellent review article on the treatment of diabetes mellitus with diet and insulin and the management of the acute emergencies in diabetes.

Kyle, L. H.; Meroney, W. H.; and Freeman, M. E. (*Georgetown Univ. Sch. of Med. and Walter Reed Army Hosp., Washington, D. C.*): STUDY OF THE MECHANISM OF BONE DISEASE IN HYPOPHOSPHATEMIC GLYCOSURIC OSTEOMALACIA. J. Clin. Endocrinol. & Metab. *14*:365-77, April 1954.

Evidence is presented to suggest that the demineralization of bones which occurs in association with the de-Toni-Fanconi syndrome is secondary to excessive urinary excretion of phosphorus. It appears probable that the phosphate loss is the result of reabsorption of this substance on the basis of a specific renal tubular abnormality. Lack of response to vitamin D therapy in patients with the Fanconi syndrome may be attributed to the fact that although this vitamin causes increased calcium retention, it also increases the urinary excretion of phosphate. Acceptance of the probability that decreased tubular reabsorption of phosphorus is the cause of bone disease in the Fanconi syndrome allows provision of examples of each of the theoretical causes of malacic bone disease.

Lazarus, Sydney S.; Goldner, Martin G.; and Volk, Bruno W. (*Div. of Labs. of Med., Jewish Sanitarium and Hosp. for Chronic Diseases, Brooklyn 3, N. Y.*): SELECTIVE DESTRUCTION OF PANCREATIC ALPHA CELLS BY COBALTOUS CHLORIDE IN THE DOG: PHYSIOLOGIC IMPLICATIONS. Metabolism 2:513-20, November 1953.

The intravenous injection of 200 mg. of cobalt causes a selective autolysis of the pancreatic alpha cells in the dog. Repeat biopsies in the same animal show that regeneration of these cells begins after five days. A single injection of cobalt elicits a transient hyperglycemia in the normal, the alloxanized, the pancreatectomized, and the partially eviscerated animals. Despite marked alpha cell damage, persistent hypoglycemia was not observed in normal animals nor was amelioration of the diabetes of alloxanized animals. This suggests that the alpha cells do not produce a principle that is physiologically active in blood sugar homeostasis and also that the severity of the diabetes of alloxanized animals is not related to the presence of the alpha cells.

Lazarus, Sydney S.; and Volk, Bruno W. (*Div. of Labs., Jewish Sanitarium and Hosp. for Chronic Diseases, Brooklyn 3, N. Y.*): STUDIES ON HYPOGLYCEMIA RESPONSIVENESS. Metabolism 2:500-09, November 1953.

A systematic attempt has been made to differentiate the mechanisms involved in the recovery phase of the blood sugar level as observed in the insulin tolerance test. This phenomenon, which is termed "hypoglycemia responsiveness," has been variously attributed to the insulin antagonistic action of the hypophysis, the adrenal cortex or medulla, the alpha cells of the pancreas, or the sympathetic nervous system. However, definite hypoglycemia responsiveness was observed in the growth-hormone-pretreated adrenalectomized animal, the ACTH-treated hypophysectomized animal, the adrenodemedullated animal, the pancreatectomized animal, the totally sympathectomized animal, and also in animals treated with various autonomic blocking agents. This leads to

the inference that the mechanism for hypoglycemia responsiveness is a direct response of the liver by glycogenolysis to hypoglycemia.

Lazarus, Sydney S.; Volk, Bruno W.; and Co Tui (*Jewish Sanitarium and Hosp. for Chronic Diseases, Brooklyn, N. Y., and the Creedmoor Inst. of Psychobiologic Studies, Queens Village, N. Y.*): ROLE OF PANCREAS IN HYPOGLYCEMIA RESPONSIVENESS AND ASSOCIATED RISE OF CIRCULATING EOSINOPHILES. Proc. Soc. Exper. Biol. & Med. *81*:288-91, October 1952.

In the pancreatectomized animal the intravenous administration of both commercial, crystalline insulin and insulin free of hyperglycemic factor is followed by a rise of the absolute eosinophile count and associated decline of the blood sugar level with a subsequent rise, similar to that observed in the normal. This is interpreted to signify that the hyperglycemic factor of the pancreas is not part of the mechanism for hypoglycemia responsiveness.

Long, W. Newton; Hartmann, William L.; Futcher, Palmer H.; and Eastman, Nicholson J. (*Depts. of Obstetrics and Medicine, Johns Hopkins Sch. of Med. and Hospital, Baltimore, Md.*): DIABETES MELLITUS AND PREGNANCY. Obst. & Gynec. *3*:160-68, February 1954.

One hundred and eighteen viable pregnancies, followed in 96 diabetic women in the Johns Hopkins Hospital from January 1, 1942, to December 31, 1952, have been analyzed. By improved diabetic control, together with the increased use of cesarean section prior to the end of the thirty-eighth week, substantial improvement in maternal and infant outcome has been achieved. No endocrine therapy was employed in 115 of these pregnancies. There was one maternal death. The uncorrected fetal and neonatal mortality in the 56 most recent pregnancies was 18 per cent. Thirty-two prenatal deaths have been analyzed from the point of view of preventability, and 59 per cent classified as preventable.

Loyke, H. F.; and Hoobler, S. W. (*Dept. of Internal Med. and the Sect. of Neurosurgery, Univ. of Michigan Med. Sch., Ann Arbor, Mich.*): EFFECT OF SPLANCHNICECTOMY OF THE HYPOGLYCEMIC AND EOSINOPENIC RESPONSE TO INSULIN. Am. J. M. Sc. 227:304-11, March 1954.

Since insulin hypoglycemia has been shown in animals to evoke epinephrine release only in the presence of intact sympathetic innervation, this test was applied to normotensive and to hypertensive subjects before and after splanchnicectomy, eosinopenia being taken as evidence of reflex secretion of epinephrine.

When an adequate hypoglycemic stimulus was produced, hypertensive and normotensive subjects did not differ strikingly in their response. Patients examined before and after splanchnicectomy showed a relative resistance to insulin hypoglycemia in the early postoperative period, with a consequent failure to develop eosinopenia.

Hypertensive subjects who had undergone splanchnicectomy one or more years previously were divided into "good" and "poor" results according to the response of their blood pressure to the operation. The patients who had had a poor result exhibited the usual eosinopenic and hypoglycemic response, whereas the good result patients, despite a comparable hypoglycemia, failed to show the expected eosinopenic response. The differences between the two groups were statistically significant. Tests of pituitary-adrenal activity in some of the good result subjects revealed no significant abnormalities.

The mechanism of insulin-induced eosinopenia is uncertain, since the response was also observed in an adrenalectomized subject. However, it is presumed, on the basis of animal studies and clinical observations, that reflex release of epinephrine is at least one cause of the eosinopenia to insulin.

If this explanation be correct, it is possible that good results following surgery are associated with effective denervation of the adrenal medulla. The clinical observation that sympathectomy leads to decreased nervousness, a gain in weight, and a reduction of the basal metabolic rate would accord with this explanation.

Magee, D. F. (*Dept. of Pharmacology, Univ. of Washington School of Medicine, Seattle, Wash.*): RELATIONSHIP BETWEEN BLOOD CHOLESTEROL AND BILE CHOLATE. Am. J. Physiol. 177:433-35, June 1954.

Transfusion of plasma containing from 600 to 1200 mg. per 100 cc. of cholesterol into bile fistula dogs produced no significant change in cholic acid output. In many cases a marked cholic acid depression was seen during the transfusion period. No change in total serum cholesterol was seen during casein-induced cholepoiesis. These results are considered to oppose the view that

conversion to cholic acid forms a major excretory pathway for cholesterol.

Marble, Alexander (*Joslin Clin. and the Baker Clin. Res. Lab., New England Deaconess Hosp., Boston, Mass.*): LATE COMPLICATIONS OF DIABETES: PREVENTION AND TREATMENT. Maryland M. J. 3:8-13, January 1954.

In the three decades since the introduction of insulin the mortality from diabetic coma has fallen steadily. With the additional aid of the sulfonamides and the antibiotics, deaths from infections and from surgical complications have been greatly reduced. The greatest problem and the greatest challenge now lie in the late complications of diabetes affecting particularly the vascular and nervous systems. Although these are found in diabetics of all ages, they are most tragic when they occur in persons in their thirties or forties who after 15, 20, or more years of diabetes are beset with retinitis seriously limiting vision, hypertension, vascular sclerosis, and nephropathy. Many of these patients will have had symptomatic neuropathy during their diabetic lives. In this group of relatively young persons death takes place most commonly from renal involvement. Duration of diabetes is important but chiefly because it allows a greater number of years for deleterious influences to operate. It is those patients with the best control who after 20 years have the fewest and least marked degenerative changes. Conversely, it is among those patients whose diabetes has been least well controlled that one finds the most distressing sequelae of long-standing diabetes. Careful, continuous control must be the aim of the physician in the care of his diabetic patients.

Margolin, Morris; and Gentry, Harold E. (*Dept. of Int. Med., Univ. of Nebraska, Coll. of Med.*): CLINICAL USE OF THE WILKERSON-HEFTMANN BLOOD SUGAR TEST. M. Times 82:185-88, March 1954.

The authors consider the test useful in a sizable majority of diabetic patients, both as an aid in diagnosis and in therapy.

McKirdie, Matthew (*Portland, Ore.*): HYPERINSULINISM DUE TO ADENOMA OF ISLETS OF LANGERHANS. West. J. Surg. 62:329-34, June 1954.

The author reviews the diagnostic features of hyperinsulinism and the findings which justify exploration of the pancreas: symptoms resembling those of insulin shock, relief on giving glucose, repeated fasting blood sugar values below 50 mg. per 100 cc., and failure to secure relief by a low carbohydrate diet.

Megibow, Raymond S.; Megibow, Samuel J.; Pollack, Herbert; Bookman, John J.; and Osserman, Kermit (*Dept. of Med. and the Physics Lab., The Mount Sinai Hospital, New York, N. Y.*): THE MECHANISM OF ACCELERATED PERIPHERAL VASCULAR SCLEROSIS IN DIABETES MELLITUS. Am. J. Med. 15:322-29, September 1953.

The authors question the concept that diabetic peripheral vascular disease is merely a severe and accelerated variety of peripheral arteriosclerosis. Their microplethysmographic investigations indicate that occlusive digital vascular disease exists at a time when there is no other evidence to suggest the presence of peripheral arteriosclerosis. Furthermore, as has been noted already, comparable studies in normal individuals have not disclosed the changes in digital hemodynamics which have been observed in diabetic patients. Therefore, it is hypothesized that the primary peripheral vascular lesion in diabetes mellitus is not arteriosclerosis but an occlusive angiopathy of the smallest vascular radicals. Although the histopathologic nature of the alterations is unknown, and although the primary localization of these lesions, whether in arteriole, capillary or venule, is undetermined, the physiologic end result is an obstruction of variable degree to the blood flow through the ultimate circulation. This, in turn, leads to increased resistance in the more central peripheral arterial bed. The anatomic expression of such hemodynamic change is accelerated vascular sclerosis.

The fact that arteriosclerosis may be more advanced in one extremity suggests that the minute vascular lesions are distributed in an irregular patchy fashion and develop at a variable rate. The alterations in the digital circulation as determined microplethysmographically, together with the characteristic lesions of diabetic retinitis and intercapillary glomerulosclerosis, suggest that the initial or fundamental vascular derangement in diabetes mellitus is limited to the smaller blood vessels. The fact that disease of the more minute channels develops in such diverse sites as the kidneys, the digits and the retinas implies that similar angiopathic disturbances might develop in other regions of the body such as the heart and brain. The data offer no clues as to the mechanisms responsible for the vascular changes described.

Mendlowitz, Milton; Grossman, Edward B.; and Alpert, Samuel (*Veterans' Administration Regional Office and Dept. of Med., The Mount Sinai Hospital, New York, N. Y.*): DECREASED HALLUCAL CIRCULATION, AN EARLY MANIFESTATION OF VASCULAR DISEASE IN DIABETES MELLITUS. Am. J. Med. *15*:316-21, September 1953.

In a study of 38 relatively young diabetic patients without overt evidence of vascular disease, persistently decreased circulation in the great toe as measured calorimetrically was the earliest demonstrable manifestation of vascular impairment in nine of the cases. Statistical evaluation of results obtained in this diabetic group and in a nondiabetic control group of 30 subjects revealed a significant decrease in blood flow in the great toe in the diabetic patients. No significant correlation could be established between cholesterol, phospholipid, or cholesterol-phospholipid ratio and the depressed circulation in the great toe; nor could any correlation be found between the duration, severity, or degree of control of the diabetes and the extent of the decrease in circulation.

Moore, Daniel C.; Carruthers, Howard C.; Bridenbaugh, L. D. (*The Mason Clinic, Seattle, Wash.*): SOME ANESTHETIC CONSIDERATIONS IN THE DIABETIC PATIENT. Bull. Mason Clin. *8*:27-35, March 1954.

A general review of some of the factors which should be kept in mind when diabetic patients are subjected to anesthesia and surgery is presented.

Moss, James M. (*Georgetown Univ. Sch. of Med., Georgetown Univ. Hosp. and Gallinger Municipal Hosp., Washington, D. C.*): USE OF VASODILATOR DRUGS IN THE TREATMENT OF DIABETIC ARTERIOSCLEROSIS OBLITERANS. Geriatrics *2*:284-87, May 1954.

In the treatment of diabetic arteriosclerosis obliterans, the author recommends Priscoline as an effective vasodilator and believes that it should be tried first. If the response is poor in full therapeutic and subtoxic doses, then Regitine should be used. The effect of Regitine closely approximates that of a sympathectomy and may be dramatic. He considers Roniacal the safest vasodilator, but since he has found its effects variable, he reserves it for use when results with the other drugs are unsatisfactory.

Näätänen, E. K.: WHY ARE LARGE INTRAVENOUS INSULIN DOSES OF WEAKER EFFECT IN THE RABBIT THAN SMALL DOSES? Duodecim. *68*:621-27, 1952. (Abstracted from Medicina Fennica *24*:47, 1952).

The author observed, when working on an insulin study, that large doses produced less effect on the rabbit than small doses. A possible explanation of this peculiar phenomenon is the assumption that a sudden increase in the level of insulin in the blood causes a very rapid and powerful reaction on the part of the pituitary and adrenals. It may be due to this powerful reaction that the effect of a large dose of insulin does not appear in full strength. In an adrenalectomized rabbit a large dose of insulin seems to produce more effect than a small dose.

Nerenberg, S. T. (*Dept. of Path., Univ. of Minnesota, Minneapolis, Minn.*): EFFECTS OF MONOSACCHARIDES AND DISACCHARIDES ON BETA CELLS OF ISLETS OF LANGERHANS. Am. J. Clin. Path. *23*:999-1001, October 1953.

Both monosaccharides and disaccharides given by mouth stimulate the secretion of insulin by the beta cells of the islets of Langerhans, as measured by regranulation of degranulated beta cells in rats. Monosaccharides given parenterally act similarly to those administered intragastrically. This group includes fructose, which has been reported as being metabolized in the animal body without the need of insulin. Disaccharides given parenterally or olive oil given intragastrically do not stimulate the secretion of insulin by the beta cells of the islets of Langerhans.

Ottaway, J. H. (*Dept. of Biochemistry, Univ. Coll., London, England*): THE INSULIN-LIKE EFFECT OF GROWTH HORMONE. Biochimica et biophysica acta *11*:443-45, July 1953.

Growth hormone can have, in certain conditions, an insulin-like effect on muscle from normal rats, but not on muscle from diabetic rats. Two explanations suggest themselves: that insulin in some way "potentiates" the tissue so that it is able to respond to the growth hormone, or that growth hormone is able to liberate insulin from a complex in which it is inactive.

Paton, A.; and Petch, C. P. (*St. Helier Hosp., Carshalton, England*): ASSOCIATION OF DIABETES MELLITUS WITH CEREBRAL TUMOR. Brit. M. J. *1*:855-56, April 10, 1954.

A 51-year-old man with no family history of diabetes had diabetic symptoms appear 3 months before the diagnosis was confirmed by a glucose tolerance test and treatment with diet and insulin started. Neurological examination was normal at the time of the tolerance test. Five weeks later, paresis of the right leg with diminished reflexes of the right knee and both ankles appeared; nine weeks after the tolerance test, rapid progression had occurred with left hemiparesis, left plantar reflex and active tendon reflexes in the legs. The spinal fluid contained 20 mg. protein per 100 cc.; the pressure was 220 mm. He became comatose and died in the tenth week after the diagnosis of diabetes. He was found to have a large glioblastoma multiform containing mainly spongioblast-like cells, in the left temporal region, spreading down into the hypothalamus but not involving the pituitary. Changes in the pancreas were noted compatible with diabetes mellitus.

A discussion of hyperglycemia and glycosuria related to experimentally produced brain lesions is given.

Patterson, John W. (*Dept. of Anatomy, Sch. of Med. Western Reserve University, Cleveland, Ohio*): HYPERGLYCEMIA AND GALACTOSE CATARACTS. Am. J. Physiol. *1*:541-43, June 1954.

Rats fed diets containing increasing amounts of galactose develop a parallel increase in blood sugar, urine sugar, urine volume, water intake and food intake. The higher the galactose intake the less the rats gain in weight per week.

Cataract formation was noted in a time related inversely to the degree of hyperglycemia. This relationship may be described by a hyperbola which is similar to the curve which illustrates the development of diabetic cataracts. Galactose, however, appears to be approximately four times as effective as glucose in the production of cataracts.

Lowering the blood sugar by the administration of phlorizin delays the development of cataracts in pair-fed rats receiving 35 per cent galactose.

Pearce, Iris A.; and Hawkes, Jean M. (*Dept. of Med., Univ. of Tennessee Coll. of Med., Memphis, Tenn.*): DIABETES MELLITUS AND DWARFISM DUE TO PRIMARY HYPOTHYROIDISM. J. Tennessee M. A. *47*:109-10, March 1954.

A case of dwarfism due to primary hypothyroidism with associated diabetes mellitus is presented. The two disturbances in endocrine metabolism appeared to be separate entities, existing concomitantly in the same individual.

Perkin, Frank S.; and Derbyshire, A. J. (*Wayne Univ. Coll. of Med., The Michigan Epilepsy Center and Harper Hosp., Detroit, Mich.*): CARBOHYDRATE METABOLISM IN THE CONVULSIVE STATE: A PRELIMINARY STUDY. Harper Hosp. Bull. *11*:248-57, Nov.-Dec. 1953.

A group of 76 patients who had proven convulsions not requiring institutional care because of severity or mental deterioration were studied over periods varying from one to seven years. The study was initiated by the observation of convulsive attacks resulting from continued hypoglycemia with resultant brain damage. Studies by repeated long term glucose tolerance tests gave results that, while indefinite and inconsistent, suggested a rather frequent abnormality of carbohydrate utilization. Studies of serum inorganic phosphorus coincident with glucose tolerance test tend to confirm this impression. The relation of current studies in labile diabetes to this problem is of interest. The effect of long-continued hypoglycemic-type diets is regarded of importance in evaluation of this problem; and, finally, the hitherto unreported high incidence of diabetes in the family history of individuals manifesting the convulsive state is, if corroborated, of utmost significance.

Perkoff, Gerald T.; and Tyler, Frank H. (*Dept. of Med. and the Lab. for the Study of Hereditary and Metabolic Disorders, Univ. of Utah, Salt Lake City, Utah*): PARADOXICAL HYPERGLYCEMIA IN DIABETIC PATIENTS TREATED WITH INSULIN. Metabolism 3:110-17, March 1954.

The authors have observed several cases of diabetes, in which the administration of increased doses of insulin was associated with deterioration of regulation and in which a decrease of the insulin administered resulted in the amelioration of hyperglycemia and glycosuria. The term "paradoxical hyperglycemia" has been chosen to describe this phenomenon for two reasons. First, it is recognized that other factors besides the one operative in these patients can produce the so-called brittle state. Second, the word "paradoxical" emphasizes the fact that the result is contrary to the primary effect of insulin, namely, a reduction in the blood sugar level.

Observations are presented in ten cases demonstrating the phenomenon of paradoxical hyperglycemia. The

clinical characteristics of this phenomenon are (a) deterioration of diabetic regulation on increasing insulin doses, (b) infrequent clinical hypoglycemic reactions, (c) cyclic glycosuria, and (d) improved diabetic regulation on reduced insulin dosage. Treatment of the elderly diabetic manifesting this phenomenon can be carried out by markedly reducing the insulin dosage. Juvenile diabetics, on the other hand, require gradual reduction of the insulin dose by very small amounts. The determination of hourly glucose excretion may prove to be a simple clinical test for the recognition of paradoxical hyperglycemia. The pathogenesis of this phenomenon is discussed. It is pointed out that many diabetic patients require large doses of insulin without manifesting paradoxical hyperglycemia.

Porter, R. W. (*Dept. of Anatomy, Univ. of California at Los Angeles Sch. of Med., and the Surgical Serv., Vet. Administration Hosp., Long Beach, Calif.*): HYPOTHALAMIC INVOLVEMENT IN THE PITUITARYADRENOCORTICAL RESPONSE TO STRESS STIMULI. Am. J. Physiol. *172*:515-19, March 1953.

Eosinopenic response to epinephrine, formalin, and histamine was measured before and after making hypothalamic lesions in cats. Anterior lesions were without effect; posterior hypothalamic lesions prevented the eosinopenic response. In other experiments, exploration stimulation of the hypothalamus was undertaken and the level of circulating eosinophils determined. Eosinopenia resulted from excitation of tuberal and mammillary areas; surrounding regions did not induce this response. These findings concur with our previously reported demonstrations of increased electrical activity in the posterior hypothalamus upon administration of stressing agents. All three lines of evidence support participation of the central nervous system in the pituitary-adrenal response.

Póvoa Filho, Hélion (*Lab. de Bioquimica da 5.a Cad. Clin. Méd. da Faculdade Nacional de Medicina. Lab. de Bioquimica do Instit. Oswaldo Cruz*): THE MAGNESIEMIA IN NORMAL AND DIABETIC BLOOD SERUM. O. Hospital *45*:307-16, March 1954.

The methods for the determination of magnesium in blood serum were reviewed, and a modification of the Denis method was proposed. The results obtained by this method in 74 cases showed that there is no significant difference between the magnesium content of the serum of diabetics and nondiabetics.

Queries and Minor Notes (*Pennsylvania*): ABNORMAL BLOOD SUGAR AND DISABILITY INSURANCE. J.A.M.A. *154*:729, February 20, 1954.

The following question was asked: At age 42, with a family history of diabetes mellitus with retinopathy and foot ulcers in my mother and a broad glucose tolerance curve, what is my prognosis?

This answer was given: The prognosis would probably be about that of an ordinary person, because knowledge of your mother's condition naturally would favor your living a sensible and cautious life. Even if you actually had diabetes at age 40, the prognosis would be for a life span three-fourths that of your average contemporaries. Control of body weight so that it approximates the standard for your age and height is the most essential protection. As for diet, limit the carbohydrate intake to 250 gm. daily and nearer 200 gm. if the dressed weight is less than 150 lb. (68 kg.). Every three months a test of the blood sugar an hour after the noon meal, together with a test for glycosuria, would be desirable.

Queries and Minor Notes (*Montgomery, W. Va.*): DIARRHEA IN DIABETICS. J.A.M.A. *154*:101, January 2, 1954.

Nocturnal diarrhea usually occurs in younger diabetic patients; but in Joslin's series of 96 cases, the ages varied from 20 to 79 years, and the average duration of the diabetes was 9 years. Previous poor diabetic control was outstanding in each instance, and diabetic neuritis preceded the diarrhea in 40 patients. The only treatment that has been found at all helpful, besides the low-residue, nonirritating diet, has been crude liver extract given parenterally.

Queries and Minor Notes (*Ohio*): DUMPING SYNDROME. J.A.M.A. *154*:100, January 2, 1954.

Exercise, unless severe and prolonged, does not cause significant hypoglycemia in a normal person. Nervous tension commonly characterizes otherwise normal persons who experience "functional" hypoglycemia some hours after a meal. The dumping syndrome is seen most

frequently after gastroenterostomy or gastric resection but has been described also in hypersensitive, overly reactive persons who had no gastric operation. Hypoglycemia is not a necessary part of the dumping syndrome, but some patients with the latter condition, whether it is of surgical origin or not, experience hyperglycemia soon after eating, followed by a reactive hypoglycemia two or three hours later. An intravenous glucose tolerance test is not abnormal in a patient with the dumping syndrome.

Queries and Minor Notes (*New York*): FAT IN THE DIET. J.A.M.A. *154*:638, February 13, 1954.

It is probable that some fat in the diet is essential for the normal adult for the following reasons: (1) to supply certain essential unsaturated fatty acids; (2) to supply adequate calories to the total food intake; and (3) to supply satiety value to the total diet. However, it takes a relatively small amount of fat (about 25 gm. a day) to satisfy these requirements. Typical American diets are high in fat, containing from 125 to 175 gm. of fat per day. A "low fat" hospital diet will contain about 50 gm. of fat per day. There would be no adverse effects of following such a diet for many years.

Queries and Minor Notes (William E. Abbott, M.D.) (*Univ. Hosp's. 2065 Adelbert Rd., Cleveland 6, Ohio*): GLUCOSE SOLUTION INTRAMUSCULARLY. J.A.M.A. *154*:1048, March 20, 1954.

Hypotension and oliguria may occur as a result of the decrease in the plasma volume (10 to 30 per cent) that follows hypodermoclysis of 2,000 ml. of a 5 per cent glucose solution in distilled water, particularly when the patient is dehydrated or if hyaluronidase is employed. It would seem unwise to administer electrolyte-free fluids to dehydrated patients by this method. Its effects are more profound when hyaluronidase is employed.

Queries and Minor Notes (*Washington*): HEMOCHROMATOSIS. J.A.M.A. *154*:1235-36, April 3, 1954.

The presented clinical data of hepatomegaly, splenomegaly, diabetes, skin pigmentation, and impotence with the high serum iron level justify a presumptive diagnosis of hemochromatosis. A liver biopsy showing considerable amounts of iron-containing pigment is the most certain procedure enabling one to confirm a presumptive diagnosis of hemochromatosis. The presence of significant amounts of iron-containing pigment in the chief cells of a specimen of gastric mucosa obtained by biopsy is almost as reliable for this purpose as a liver biopsy.

In a review of all published cases in which massive venesection was used for the treatment of hemochromatosis, Davis and Arrowsmith (Ann. Int. Med. *39*:723 October 1953) reported that 12 out of 15 patients showed a satisfactory response. The patient should be given a high protein, high carbohydrate diet with supplements of yeast and a multivitamin preparation as in other cases of hepatic cirrhosis.

Queries and Minor Notes (*Minnesota*): HYPERCHOLESTEREMIA. J.A.M.A. *155*:90, May 1, 1954.

Hypercholesteremia in a patient has significance beyond its possible role in the pathogenesis of atherosclerosis. Hypercholesteremic hyperlipemia may be present in several clinical entities, e.g., biliary obstruction, hypothyroidism, diabetes mellitus, the nephrotic syndrome, and hyperadrenocorticism (spontaneous or iatrogenic), as well as in essential hypercholesteremic (familial) xanthomatosis.

Queries and Minor Notes (*Detroit*): NPH INSULIN. J.A.M.A. *154*:728, February 20, 1954.

In accordance with previous action taken by the I.S.P. Insulin Advisory Board, isophane insulin has been designated as the name for NPH insulin, the latter term being retained as a synonym. Its blood sugar lowering action places it in an intermediate position between globin insulin and protamine zinc insulin. Isophane insulin may be mixed with regular insulin. Loss of quick action of regular insulin is less with isophane insulin than with similar mixtures of protamine zinc insulin, because isophane insulin contains less available protamine. It is not recommended for children below five years of age or for patients who require quick-acting insulin.

Reinhardt, William O.; and Li, Choh Hao (*Depts. of Anat. and Biochemistry, Univ. of California, Berkeley, Calif.*): EXPERIMENTAL PRODUCTION OF ARTHRITIS IN RATS BY HYPOPHYSEAL GROWTH HORMONE. Science *117*:295-97, March 20, 1953.

Progressively increasing daily doses of pituitary growth hormone intraperitoneally administered over a 6-month period to adrenalectomized and ovariectomized rats maintained on treatment with 1 per cent saline resulted in chronic arthritis of the knee and ankle joints, with relief on hydrocortisone therapy for one week. These observations support the hypotheses that the pituitary growth hormone may be of direct etiologic importance in the chronic arthritides and related conditions and that the ameliorative antiarthritic effects of corticotropin and cortisone may represent either suppression of pituitary-growth-hormone secretion or of antagonism to growth hormone at the tissue level or both.

Remy, M.; Cadiot, P.; and Pernot, C. (*Paris, France*): HEPARIN IN TREATMENT OF ARTERITIS OF LOWER LIMBS. La presse médicale, Paris *61*:961, July 4, 1953. (Abstr. from J.A.M.A. *153*:1130, November 21, 1953.)

Excellent results were reported following intra-arterial injections of heparin in patients with acute thrombosis superimposed on chronic arteritis of the lower limbs; amputations, which had been considered inevitable in two cases were averted. Intra-arterial injections, preferably into the femoral artery directly above the obstruction were considered essential.

Ritama, V. (*Pathological Dept. of the Kivelä Hosp., Helsinski, Finland*): AMYLOIDOSIS OF THE CEREBELLAR CORTEX IN A DIABETIC: OBSERVATIONS ON THE PATHOGENESIS OF CEREBRAL AMYLOIDOSIS. Annales medicinae internae Fenniae *43*:51-67, 1954.

In the case of an elderly man who had mild diabetes without acidosis, the essential features of the last weeks of life were a high degree of somnolence and a cyanosis which became aggravated when the patient was asleep. Though the carbon dioxide content of the blood was within normal limits, death seemed to be caused by progressive anoxemia. Autopsy revealed amyloidosis of the secondary type in the spleen and the adrenals. Amyloid was also encountered in the pancreatic islands and the renal glomeruli, with lesions characteristic of the Kimmelstiel-Wilson lesion. An interesting feature was amyloidosis of the cerebellar cortex, accompanied by capillary lesions similar to those noted in the renal glomeruli. There seemed to be reason to attribute the diabetic syndrome, the Kimmelstiel-Wilson lesion, and the amyloidosis to the same unknown cause.

Roeckel, Irene E. (*Med. and Surg. Servs. and Div. of Pathol., New York City Hosp., Welfare Island, Dept. of Hosps., New York, N. Y.*): RAPID BEDSIDE TEST FOR SERUM CHLORIDE AND BICARBONATE: A FURTHER INVESTIGATION OF SCRIBNER'S METHOD. Am. J. M. Sc. *227*:426-30, April 1954.

Determinations of serum chloride with Scribner's bedside method and Saifer and Kornblum's method showed the expected deviation of ± 2 per cent. Determinations of serum bicarbonate with Scribner's bedside method and Van Slyke's volumetric carbon dioxide method were found to be within the expected range of deviation of ± 4 vol. per cent in 81 per cent of the cases. These new methods offer inexpensive, simple, accurate bedside procedures for effective control of therapy in cases of electrolyte-acid-base disturbance.

Rose G.; Stern, I.; and Shapiro, B.: SYNTHETIC ACTIVITY OF ADIPOSE TISSUE. Acta medica orientalia *12*: 187, 1953. (Abstr. from J.A.M.A. *154*:164, January 9, 1954.)

Recently it was shown that an active metabolic process is involved in the uptake of fatty acids by adipose tissue from the medium in vitro. Glycogen deposition in adipose tissue precedes fat deposition. Direct evidence for the assumption that adipose tissue is capable of fat synthesis was furnished by in vitro experiments involving the incubation of adipose tissue in a medium enriched with heavy water.

Rose, S. (*Australia*): EFFECT OF DESOXYCORTICOSTERONE ACETATE ON DIABETIC KETOSIS. Australian J. Exper. Biol. and M. Science *31*:273, June 1953. (Abstr. from J.A.M.A. *153*:1485, December 19, 1953.)

It has been suggested that part of the insulin resistance and aggravation of the diabetic state that occurs during diabetic ketosis is related to the overactive adrenal cortex, with consequent overproduction of 11, 17-oxysteroids. Desoxycorticosterone acetate partially suppresses this increased adrenal activity but not to the same extent as insulin. Desoxycorticosterone acetate administration to diabetic, ketotic rats causes a fall in blood sugar, which may be related to the partial suppression of adrenal activity and consequent decline in production of 11, 17-oxysteroids.

Segal, Jacob A. (*Manchester Memorial Hosp., Manchester, Conn.*): SILENT MYOCARDIAL INFARCTION. Conn. M. J. 17:904-08, November 1953.

Myocardial infarction may occur without pain. The author quotes Hipp, who reported 150 cases of recent myocardial infarction with eleven cases in which no history of pain was obtained. Five of these patients were either psychotic, in diabetic coma, in diabetic acidosis, or in coma due to cerebral embolus.

Sharkey, Thomas P. (*Ohio State Univ. Coll. of Med., Columbus, Ohio*): DIABETES MELLITUS AND OBESITY. Ohio M. J. 49:986-90, November 1953.

An excellent short review is given of the relationship between diabetes and obesity, with a more detailed summary of recent animal experimentation with strains of mice showing hereditary obesity and diabetes.

Sheppe, William M.; and Sheppe, William M., Jr. (*Dept. of Med., The Wheeling Clin., Wheeling, W. Va., and the Dept. of Psychiatry and Neurology, Univ. of Virginia, Charlottesville, Va.*): THE PSYCHOGENIC PROBLEMS OF THE YOUNG DIABETIC PATIENT. West Virginia M. J. 50:65-69, March 1954.

The stresses of life precipitate emotional swings in young diabetics, which, in turn, may activate profound physiologic disturbances, with subsequent loss of diabetic control. Recognition of this fact does not simplify the treatment of the disease, but it does provide one more tool in the struggle to overcome the metabolic instability of the young diabetic. Factors to be dealt with include personality deviations, immaturity, personal and family relationships, and the environment in general.

Shingleton, William W., and Anlyan, W. G. (*Dept. of Surg., Duke Univ. Sch. of Med., Durham, N. C.*): CHRONIC RELAPSING PANCREATITIS. South. M. J. 47: 451-54, May 1954.

Chronic relapsing pancreatitis is a not uncommon condition producing recurring attacks of upper abdominal pain and possessing a wide variety of serious complications. Diagnosis can usually be established by intelligent evaluation of the clinical picture along with laboratory findings, of which the secretin test is most helpful. The treatment of the condition, when symptomatic, is surgical. Several surgical procedures have yielded favorable results, but no single procedure has been uniformly successful in all cases. Based on certain anatomic and physiologic observations in animals and early clinical results in the human celiac, ganglionectomy appears to be the surgical procedure of choice for relief of pain in relapsing pancreatitis.

Shull, Kenneth H.; Mann, George V.; Andrus, Stephen B.; and Stare, Fredrick J. (*Dept. of Nutrition, Harvard Sch. of Public Health, and the Depts. of Biochemistry, and Pathology, Harvard Med. Sch., Boston, Mass.*): RESPONSE OF DOGS TO CHOLESTEROL FEEDING. Am. J. Physiol. 176:475-82, March 1954.

Ten mongrel dogs were fed purified diets containing alphaprotein or casein at a level of 20 per cent and varying amounts of cholesterol of from 1 to 30 per cent. DL-methionine was added to one alpha-protein diet. A "natural" diet consisting of cholesterol-coated dog pellets was also studied. These diets induced hypercholesteremia in all animals assayed. The serum cholesterol levels of the animals fed the experimental diets showed marked fluctuations from week to week in spite of constant cholesterol intakes. There was great individual variation in the hypercholesteremic response of the animals to the quantity of cholesterol ingested. In contrast to similar studies done with monkeys, there was no clear evidence to indicate that the sulfur amino acid-deficient alpha-protein diets induced greater hypercholesteremia than did such diets supplemented with methionine or diets containing casein. Although all classes of lipoproteins measured including the S_f 12-20 lipoproteins were grossly elevated in the animals fed the experimental diets, no atherosclerosis was found in the four animals that were autopsied after periods of 11 to 22 weeks of severe hypercholesterolemia and hyperlipoproteinemia.

Silbert, Samuel (*Montefiore Hosp., New York, N. Y.*): SURGICAL CONSIDERATIONS IN THE TREATMENT OF INFECTION AND GANGRENE IN THE DIABETIC. Conn. M. J. 17:895-903, November 1953.

The author reviews the problems of arteriosclerosis and susceptibility to infection of diabetics. He cautions against any surgery using local anesthesia in the extremities of a diabetic. Damage results very quickly in the diabetic, and failure to open an infected wound or relieve tension may result in extensive gangrene within twenty-four hours. Local heating of the tissues by the

use of large baking lamps or diathermy is dangerous. The harm caused by overheating tissues with poor blood supply is still not generally appreciated. A temperature between 90° and 95° F. maintained for several hours is an effective and safe form of treatment. The operative mortality of midleg amputation is much lower than that of thigh amputations; rehabilitation is made much easier because of preservation of the knee joint, and persistent stump pain is a very infrequent complication. Leg stumps are usually painless, and it is a noteworthy advantage of amputation below the knee.

Sinkoff, M. W.; De Bodo, R. C.; Den, H.; and Kiang, S. P. (*Dept. of Pharmacol., New York Univ., Coll. of Med., New York, N. Y.*): ANTI-INSULIN ACTION OF GROWTH HORMONE IN THE ADRENALECTOMIZED-HYPOPHYSECTOMIZED DOG. Am. J. Physiol. *176*:361-66, March 1954.

Administration of growth hormone ameliorated or abolished the severe insulin hypersensitivity of adrenalectomized-hypophysectomized dogs maintained on small doses of DCA. Concomitantly growth hormone ameliorated or abolished the secondary hypoglycemia of the glucose tolerance tests and retarded the rapid rate of fall of the blood sugar to hypoglycemic levels. Growth hormone did not produce insulin resistance or diabetes in the adrenalectomized-hypophysectomized dogs. It is concluded that: (a) the corticotropin content of growth hormone preparations is not responsible for the actions of growth hormone on carbohydrate metabolism, and (b) the adrenocortical steroids are not essential for the actions of growth hormone on carbohydrate metabolism.

Siperstein, M. D.; Nichols, C. W., Jr.; and Chaikoff, I. L. (*Dept. of Physiol., Univ. of California Sch. of Med., Berkeley, Calif.*): EFFECTS OF FERRIC CHLORIDE AND BILE ON PLASMA CHOLESTEROL AND ATHEROSCLEROSIS IN THE CHOLESTEROL-FED BIRD. Science *117*:386-89, April 10, 1953.

The authors report that bile administration enhances the rise of plasma cholesterol in rats and the severity of the associated atheromata resulting from cholesterol feeding. Both of these effects to a major degree can be prevented by the feeding of ferric chloride. It is likely, although not proved, that the iron acted by precipitating bile salts in the intestinal tract. The action of bile in facilitating the appearance of atheromata in the cholesterol-fed bird correlated with an earlier finding that bile controls the rate of cholesterol absorption by the intestine. This raises the question of the role played by intestinal bile in the development of arteriosclerosis in man. The above-reported results suggest that the binding of bile salts in the intestinal tract with the suppression of cholesterol absorption may offer a means of controlling the development of arteriosclerosis.

Speirs, Robert S. (*Roscoe B. Jackson Memorial Lab., Bar Harbor, Me.*): EOSINOPENIC ACTIVITY OF EPINEPHRINE IN ADRENALECTOMIZED MICE. Am. J. Physiol. *172*:520-26, March 1953.

The authors report that a decrease in the number of circulating eosinophils was observed three or four hours following an injection of epinephrine in 133 of 213 adrenalectomized mice. In this group, 45 per cent of the animals responded with an eosinopenia of 30 per cent or more. This eosinopenic response was correlated with the presence of accessory adrenals or in a few cases with remnants of the adrenal cortex. The data reported were obtained from C_{57}BR/cd mice, but preliminary surveys indicated that accessory adrenals were also found in other strains of mice. During a period of 75 days after adrenalectomy, the eosinopenic response to epinephrine was found to increase progressively. This response was not affected by castration. Following an injection of epinephrine, the eosinophils of adrenalectomized mice failed to respond to a second injection of epinephrine administered 3 hours later. This refractory period occurred in all mice, including those possessing adrenal remnants. The epinephrine-pretreated mice did not show an eosinopenic response to corticotropin, histamine, insulin, oils, and various toxic materials. However, a quantitative response was obtained to adrenal 11-oxycorticosteroid hormones. Thus, the eosinophils of epinephrine-pretreated mice were capable of responding to cortisone but did not respond to epinephrine. This indicates that epinephrine must not act directly on the eosinophil cells but instead acts indirectly through a release of hormone from adrenal cortical tissue.

Steinborn, Kurt (*Universitäts-Kinderklinik Hamburg-Eppendorf*): EXPERIMENTS IN TREATMENT OF DIABETIC KETONEMIA. Klin. Wchnschr. *31*:633-37, July 15, 1953.

Eighteen cases of acetonemic diabetic children and juveniles were treated orally with substances producing pyroracemic acid (alanine, lactic acid) and with pyroracemic acid itself. In 14 cases the urine was free of

acetone one to three hours after the start of the treatment, in one case several hours later. In 3 cases the therapy failed. The possibility is pointed out of treating in a similar manner other nondiabetic acetonemias.

Stokes, John H.; Beerman, Herman; and Ingraham, Norman R., Jr. (*Univ. of Pennsylvania Depts. of Dermatology Sch. of Med., Philadelphia, Pa.*): DERMATOLOGY AND SYPHILOLOGY: WEBER-CHRISTIAN SYNDROME. Am. J. Med. Sci. 225:446-62, April 1953.

The author reviews briefly the broad field of fat necroses and delineates the particular features of relapsing, febrile, nodular, nonsuppurative panniculitis—the so-called Weber-Christian syndrome.

Sturtevant, F. M.; and Fuller, Nancy E. (*G. D. Searle & Co., Chicago, Ill.*): A SIMPLIFIED TEST FOR ANTI-DIABETIC ACTIVITY. Endocrinology 54:561-64, May 1954.

The index of severity of alloxan-diabetes in rats was established as that percentage of food consumed which is excreted as glucose and is not related to body weight or food intake.

Tamchès, A. (*Paris, France*): ANTIATHEROMATOUS PROPERTIES OF HEPARIN: CLINICAL AND BIOLOGICAL PROOFS. La presse médicale, Paris 61:1382, October 24, 1953. (Abstr. from J.A.M.A. 154:455-56, January 30, 1954.)

The author asserted in 1949 that heparin has angiotrophic and angiospasmolytic properties in addition to its anticoagulant function. In the present work, he now credits heparin with an antiatheromatous property.

Treuting, Theodore F. (*Dept. of Med., Tulane Univ. of Louisiana Sch. of Med., New Orleans, La.*): THE EFFECT OF THE EMOTIONS ON THE PERIPHERAL CIRCULATION. Am. J. M. Sc. 227:94-101, January 1954.

The author reports upon the use of plethysmography in the study of patients with cardiovascular diseases, indicates a correlation between the type of plethysmographic tracing and the disease entity, and confirms objectively the old observation that peripheral blood vessels are easily influenced by psychic factors.

Vosschulte, K.; and Becker, W. H. (*Giessen, Germany*): THE PROBLEM OF SURGICAL MANAGEMENT OF HYPOGLYCEMIA PRODUCED BY TUMORS OR HYPERPLASIA OF THE ISLET CELLS. Deutsche med. Wchnschr. 78:185, February 6, 1953.

The authors present a review of 350 cases of hyperinsulinism caused by tumors or hyperplasia of the islet cell tissue. It is significant that a palpable tumor was not found in 38 per cent of patients explored surgically. However, in one-fifth of these patients, single or multiple adenomas were found by microscopic study after resections of one-half to two-thirds of the tail and body of the pancreas.

Weichselbaum, Theodore E.; Margraf, Harry W.; and Elman, Robert (*Dept. of Surg., Washington Univ. Sch. of Med. and Barnes Hosp., St. Louis, Mo.*): METABOLISM OF INTRAVENOUSLY INFUSED FRUCTOSE IN MAN. Metabolism 2:434-49, September 1953.

During and after infusion of fructose in humans and in dogs, whole blood and plasma have been analyzed for their content of fructose, glucose, lactic and pyruvic acids, carbon dioxide content, and *p*H. Specimens of muscle and skin have also been analyzed for fructose and glucose, and specimens of muscle and liver for glycogen.

Wells, R. H. C. (*Univ. of Malaya, Ma'aya*): THE MANAGEMENT OF DIABETES MELLITUS. Proc. Alumni A. Malaya 6:214-20, December 1953.

A scheme is presented for the management of diabetics based on recent advances in the understanding of the basic metabolic defects in diabetes in accordance with modern practice, at several large diabetic clinics.

Zimmerman, Hyman J.; Parrish, Alvin E.; and Alpert, Louis K. (*Dept. of Med., V. A. Hosps., Omaha, Neb., and Washington, D. C.*): EFFECT OF ACTH ON RESPONSIVENESS TO INSULIN. Metabolism 2:424-33, September 1953.

The effect of corticotropin (ACTH) on the insulin sensitivity of 17 patients was studied. In only 4 of this group of 17 patients was there any significant loss of sensitivity. The possible significance of these results is discussed.

EDITORIALS

THE RESPONSIBILITIES OF THE DIABETICS' PHYSICIAN

The lifetime care of the diabetic patient presents the physician with great responsibilities. Because of the very uniqueness of diabetes, these responsibilities cannot be ignored even though frequently they will tax his capacities. In no other chronic disease is it so imperative for the patient to understand the principles of treatment and to apply his knowledge day by day. To an unusual degree the character, temperament, and philosophy of the individual influence his fidelity to treatment and his ultimate health and longevity. Furthermore, the vicissitudes of life are extremely likely to affect the behavior of the disease and to demand emergency changes in the program. In no other disability is there a need for a closer relationship between the physician and his patient whose lifetime may, and indeed often does, exceed his own.

Are we fulfilling our obligations to the patient? To be specific, are we training him adequately in the technical phases of daily care? Does he know food values and diet calculation? Will he have a practical understanding of diabetes and how it may affect his future? Does he know how to prevent diabetic acidosis? Has he been made to appreciate the importance of good control and the part it plays in the complication story? Do we as physicians take the trouble to understand him as a person, to know his worries and frustrations and his home environment? And, with this information as a background, do we then help him to develop a philosophy which will smooth the rough spots of his lifetime with diabetes?

Unfortunately, we must give a negative answer to most of these questions. Our technical training of the patient tends to be cursory; first, because we delegate the duty to persons who are apt to regard the work as another chore; and second, because we assume that the patient knows more than he does. We fail to arrange a plan for subsequent care that is economically practical for him, and therefore lose the opportunity for adequate supervision and counseling, so imperative during his first year of treatment. And it is a common fault to permit our preoccupation with the scientific phases of diabetes to overshadow our interest in the human side of the problem.

For these and other reasons we fail in our efforts to help the patient achieve an ideal objective—a long, comfortable, and useful life. These achievements are never possible for a person who makes little or no effort to keep his diabetes controlled. This statement brings us inevitably to the question, "What constitutes diabetic control?" In some circles freedom from symptoms of glycosuria and maintenance of weight are considered criteria for control. In other areas chemical control is sought. In between the two extremes is a reasonable concept which admits that it is undesirable to attempt to keep the labile diabetic sugar-free, but that one should permit as little glycosuria as possible consistent with freedom from severe insulin reactions. Failure to differentiate clearly between this group and the larger insulin-tolerant group has led to a state of confusion in the minds of many practitioners, with the result that control in this group (usually easy to obtain) is not sought.

A philosophy that maintains that diabetes and vascular degeneration are part and parcel of the same disease, and that complications are inevitable despite control if the patient lives long enough, has gained too many followers. This pessimistic attitude ignores completely the contrary evidence; that is, the growing number of twenty-five-year duration diabetics who are free from vascular disease. We are seeing too many tragic examples of the fact that insulin has kept many diabetics alive, but not controlled, long enough for vascular complications to develop. We feel that we do not have the right to jeopardize the future health of our patients by compromising with indifferent control. We have a strong conviction that this attitude is more justifiable and reasonable than the policy of those who take a defeatist position.

The time is long since past when strong emphasis should have been put on the need for higher ideals in

treatment and standards of health for the diabetic. If we as physicians do not urge higher standards for our patients, how can we expect them to strive for them? We need a renaissance in the importance of diet. The diabetic on insulin is living on a subsidy, so to speak, and like people and industries which survive largely because of this type of help, is prone to do as little as possible to help himself.

What qualities must a physician have who accepts the obligations we have discussed? Certainly he should be a man who can face the problem in its broadest aspects and at the same time not be annoyed by details. Furthermore, he should possess infinite patience. It is one thing to maintain an enthusiastic interest in the patient's physical and emotional problems. It is still another thing to instill and perpetuate this attitude in the patient's mind throughout his life. In the apt words of Randall Sprague in his presidential address at the San Francisco meeting, he must administer care for the patient with "warm-hearted compassion."

We are facing an obligation of our own making. Its breadth and depth give it great magnitude, but perhaps its very continuity gives us a feeling of inadequacy in fulfilling the obligation.

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DIABETIC NEUROPATHY

In discussions regarding the long-term effects of diabetes, vascular complications are often stressed without adequate mention of other influences of the disease. Judging from end results, the effect of inadequately controlled diabetes on the body is a general one, including a widespread deleterious influence not only on the vascular but also on the nervous system. Emphasizing the not infrequent coexistence of retinopathy, nephropathy and neuropathy, Root (paper before Section of Medicine, American Medical Association, San Francisco, June 22, 1954) has suggested the term "diabetic triopathy."

It is likely that diabetic neuropathy represents a general effect, although the prominent signs and symptoms are most often those of a peripheral "neuritis" involving particularly the lower extremities. In certain patients, as Goodman points out in an article elsewhere in this issue, the manifestations appear to arise chiefly from affection of the femoral nerve. In such cases, pain and tenderness, paresthesias and muscular weakness all reflect the distribution of this nerve. Absence of the patellar tendon reflexes and a positive femoral nerve stretch test (Lasègue's sign in reverse) are other diagnostic points emphasized by Goodman. However, as in Goodman's cases, femoral or other peripheral nerve involvement is often accompanied, followed, or even preceded by other manifestations of neuropathy including "neuropathic foot," paresis of the urinary bladder, "diabetic diarrhea" and postural hypotension. Perhaps paralyses of extraocular muscles should also be included. In patients with diabetic neuropathy, increase in the total protein of the spinal fluid is often found without increase in cells.

As stressed by Goodman, meticulous and consistent control of diabetes is the most important measure in treatment. If histories are carefully taken it will be found that, almost without exception, control of diabetes has been poor prior to the development of neuropathy. It is true that when patients present themselves for treatment the diabetic condition may be under good control and casual questioning will show that this situation has prevailed for some days or weeks. However, more persistent examination will reveal that a long period of neglect preceded this. Then with development of symptomatic neuropathy, the patient on his own took steps to bring the diabetic condition under control only to find that after some weeks the symptoms of neuropathy persisted. Only after this was the physician consulted.

It goes without saying that along with careful control of diabetes, a diet thoroughly adequate in protein, vitamins, minerals and calories should be provided. It is reasonable to supplement the diet with preparations containing vitamin B complex, although no striking beneficial effect should be anticipated from such medication.

When patients with severe pain down the extremities (often worse at night), marked hyperesthesia of the skin, and weakness respond in two or three weeks to the treatment described above, the problem is relatively simple. The patients who "try the soul" of the physician are those who, after weeks and months of careful control of diabetes, still are miserable with persistent symptoms. They represent the real problem of diabetic neuropathy and these are the patients with whom all would welcome more specific therapy. True, experience has shown that in time almost all patients become comfortable (although residua of hypesthesia, impairment of vibratory sense, etc., may be left) and the physician may with confidence give an ultimately good prognosis. However, the patient tires of the weeks or months of continued discomfort and partial disability. The list of agents tried over the years is a long one: vitamin B complex given orally or parenterally, crude liver extract, BAL, pregnant mammalian liver extract and vitamin B_{12}. Physicians who have treated large numbers of patients

over the years can recall certain patients with whom each of these measures seemed to be successful. However, with none of them is relief obtained with any significant degree of uniformity; and in a situation in which various agents appear curative, it is doubtful if any is specific. The last word in the management of diabetic neuropathy remains to be said and the present state of the problem presents a real challenge to all interested in diabetes.

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GALACTOSEMIA, OR GALACTOSE DIABETES

Galactosemia, sometimes called galactose diabetes, is caused by an inborn error of metabolism that leads to inability of the body tissues to utilize galactose. The disorder is characterized by the appearance of a reducing substance in the urine, often mistakenly thought to be glucose but easily identified as galactose, an elevated level of galactose in the blood if the diet includes galactose (as in milk), and concomitant pathologic changes in various organs. First described by von Reuss in 1908,[1] there are now approximately 35 cases reported, but undoubtedly the incidence is much higher than these reports indicate. Since 90 per cent of the recognized cases have been under one year of age, its diagnostic importance mainly concerns physicians who care for infants and children. In an infant under one year of age with reducing substance found in the urine, the diagnosis of galactosemia should be considered before that of diabetes mellitus.[2]

The metabolic defect appears to be in the enzymes that convert galactose to glucose-1-phosphate, either galactokinase or Waldenase:[3]
adenosinetriphosphate + galactose (+ galactokinase) → galactose-1-PO_4 + adenosinediphosphate (+ Waldenase) + uridine-diphosphoglucose (coenzyme) → glucose-1-PO_4 (+ phosphorylase) → Glycogen + PO_4.

Pathologic anatomic changes are most prominent in the liver. In the active stage of the disease, areas of cellular degeneration and necrosis are found, with bile stasis and a peculiar abnormal pseudoacinar grouping of the hepatic cells, sometimes with fatty metamorphosis.[4] In untreated or advanced cases, two types of cirrhosis may appear—the micronodular Laennec's type, and cirrhosis associated with post-necrotic scarring. In the kidneys, the tubular epithelium is swollen, containing what is usually described as glycogen but might be galactogen. In the eyes the lenses often show lamellar or nuclear cataracts.

The cause of these pathologic cellular changes is debatable. Mason and Turner[5] blamed the lowering of blood glucose. But the absence of similar cellular damage in disorders such as glycogen storage disease and hyperinsulinism, associated with low blood sugar, makes this hypothesis doubtful. Several authors have suggested[6, 7] that the elevated blood galactose was a direct cause of the pathologic cellular abnormalities. Some investigators[8, 9] have produced lens opacities in rats by feeding large amounts of galactose. Dam's experiments[10] with the feeding of galactose to chicks led him to the conclusion that galactose damaged the central nervous system. Craig and Maddock[11] have described the production of lens opacities by high galactose diet in rats, associated with failure of growth, increased urinary nitrogen and amino-aciduria, but without hepatocellular changes. The occurrence of abnormal amino-aciduria with galactosemia[12, 13] suggests that the losses of certain essential lypotropic amino acids, due to abnormal renal tubular function, might lead secondarily to some of the pathologic changes in the liver.

Although symptoms of the disorder have been noted usually after an affected infant was given milk feedings, some observers assert that tissue damage may occur in utero.[14, 15] In most patients the symptoms appear at one or two weeks, but in others not until two or three months of age. Persistent jaundice often exists, followed or accompanied by gastrointestinal difficulties, regurgitation, and occasionally diarrhea with yellow stools. The infant often fails to gain weight after being offered several dietary formulae. Drowsiness, lethargy and convulsions may occur. A direct or collateral family history of this disorder may be elicited in approximately 30 per cent of the cases and several reports describe the disease in siblings.[16-18] There is no apparent sex linkage.

The most common physical findings are dystrophy, icterus, pallor, hepatomegaly and lamellar cataracts. Less common findings are splenomegaly, ascites, petechiae with hemorrhagic tendency. Roentgenograms of the long bones may reveal osteoporosis. A loss of the Moro response and absence of tendon reflexes may suggest damage of the central nervous system.

Laboratory tests usually reveal elevated blood galactose, albuminuria and mellituria, often associated with a normocytic hypochromic anemia. The urinary reducing substance is identified as galactose by the formation of the osazone, and mucic acid recovery, and by chroma-

tography.[15, 19] Liver function tests may show positive cephalin flocculation, elevated thymol turbidity, direct bilirubin reaction and prolonged prothrombin time. The non-protein nitrogen of the blood may be elevated. The glucose tolerance is usually normal but the galactose tolerance test reveals a prolonged high blood galactose curve, often with a reciprocal fall in blood glucose. This fall, sometimes extreme, may be a contraindication to the performance of the galactose tolerance tests. After a galactose tolerance test, existent amino-aciduria may increase; also, in a treated case, free of symptoms, the performance of a galactose tolerance test may provoke the reappearance of amino-aciduria.[20, 21]

After the diagnosis is established, treatment is mainly directed to the omission of lactose from the diet. After the elimination of milk, with substitution of casein hydrolysates (as amigen), the urine becomes free of galactose usually within 24 hours, and the level of blood galactose diminishes. The infant begins to gain weight and, varying with the severity of antecedent liver damage, the jaundice disappears. The administration of amino acid mixtures may serve to replace losses of essential amino acids in the urine.[13] Several investigators[22-24] found that when glucose was given with galactose, the galactosemia and galactosuria was less than when galactose was given alone, perhaps owing to decreased absorption of the galactose. Some found[25] that if glucose metabolism was accelerated by giving glucose or insulin, galactose tolerance was improved.

The deleterious effects of this disorder increase with its duration, but if it is recognized and treated early, the prognosis is good. The dramatic prompt disappearance of its various manifestations, which follows appropriate treatment, is a most rewarding experience for the responsible clinician. Both liver damage and cataracts appear to be reversible even when far advanced. In many cases mental retardation seems to be persistent. The first case reported in America by Townsend, Mason, and Strong,[17] when reassessed at 16 years of age, had an I.Q. of 64. Long after all signs and symptoms of the disorder disappear, with successful treatment, the galactose tolerance test reveals intolerance for galactose.

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BOOK REVIEWS

DIABETIC MANUAL FOR THE DOCTOR AND PATIENT. *By Elliott P. Joslin, M.D., Sc.D. $3.00, pp. 315, ninth edition. Lea and Febiger, Philadelphia, Pa., 1953.*

DIABETIC CARE IN PICTURES. SIMPLIFIED STATEMENTS WITH ILLUSTRATIONS PREPARED FOR THE USE OF THE PATIENT. *By Helen Rosenthal, B.S., and Joseph Rosenthal, M.D. $3.00, pp. 164, second edition. J. B. Lippincott Company, Philadelphia, Pa., 1953.*

HANDBOOK FOR DIABETIC CHILDREN. *By Alfred E. Fischer, M.D., and Dorothea L. Horstmann. $1.75, pp. 64. Intercontinental Medical Book Corp., New York, N. Y., 1954.*

As the knowledge of diabetes grows, it becomes increasingly apparent that good control of the disease is necessary to prevent, or at least delay the development of certain serious complications. In order to have good control, the patient must understand his disease and cooperate with his physician. This, in turn, creates a demand for textbooks, authoritative enough to cover the subject, clear enough to be understood by the educated and unlettered alike, and written in a way to arouse enthusiastic cooperation. New editions of three such books have recently been published.

The publication of the ninth edition of Joslin's "Diabetic Manual" is proof in itself of the success of this particular book. Written in a form that follows closely that of previous editions, it gives in a clear and concise form the information essential for a diabetic patient. The illustrations are interesting; the language is friendly and personal; the general feeling of the book is one of encouragement. That a happy, disciplined and useful life is not incompatible with diabetes is stressed throughout the book. It tends to give, probably as much as any book can give, the radiant enthusiasm and encouragement which has been the outstanding characteristic of Dr. Joslin's relationship to a large number of devoted patients over the years.

The second edition of "Diabetic Care in Pictures" by Helen and Joseph Rosenthal demonstrates once again the truth of the old adage, "One picture is worth ten thousand words." The numerous photographs, charts and diagrams make this a first-rate teaching manual for the child or adult with diabetes. The section devoted to the diet plan with interchangeable food exchanges continues the pictorial form used in their first edition. For those whose patient group includes many who have a limited grasp of the English language, this pictorial, primer type of teaching is highly recommended.

The manual of Fischer and Horstmann is a relatively new addition to the enlarging library for the diabetic layman. Written presumably for children and for those concerned with the care of juvenile diabetics, it would be of value to an adult with diabetes. Although it lacks illustrations, this is compensated for, at least in part, by the conciseness of the book. Within the limits of 64 pages, this paper-bound book provides a wealth of information for the child and his parents.

While these books have been written primarily for the patient, each has certain features that recommends it to the attention of the physician. In the last analysis, the education of the diabetic patient must be the task of the doctor. Every aid that he can receive from those experienced in teaching the diabetic patient should improve his own technics. Consequently, each of these books should find a place on the office bookshelf of the physician whose responsibility is the care of patients with diabetes mellitus.

THE PRACTICAL MANAGEMENT OF DIABETES: *By Edward Tolstoi, M.D., Associate Professor of Clinical Medicine, Cornell University Medical College; Attending Physician and Chief, Diabetic Hospital, The New York Hospital; Consulting Physician, New York Infirmary for Women and Children; Consulting Physician, The Norwalk Hospital, Norwalk, Conn. $3.25, pp. 88. Charles C. Thomas, Springfield, Ill., 1953.*

The book contains an exposition of the method of treatment advocated by the author who contends that dietary regulation of diabetes is unnecessary so long as sufficient insulin is used to prevent symptoms, avoid acidosis and maintain weight. He claims that patients treated in this way manage just as well as those whose physicians make a strong effort to control glycosuria and hyperglycemia. He considers the efforts made by most physicians treating diabetics to check glycosuria, to abolish or to minimize glycosuria and hyperglycemia, to be needless and undesirable. On the other hand, the majority of physicians who have had long experience in the treatment of diabetes and its complications almost always report that they find the patient who neglects dietary regulation is definitely more subject to impairment of health and the development of complications. According to their viewpoint, Tolstoi's book would give less experienced physicians a feeling of false security.

Herman Otto Mosenthal

Second President of the American Diabetes Association 1941-42

George E. Anderson, M.D., Brooklyn, New York

Herman Otto Mosenthal, a founder and the first president of the New York Diabetes Association in 1935, and also the second president of the American Diabetes Association, died on April 24, 1954.

Dr. Mosenthal was born in New York City on July 8, 1878. He was the son of Joseph Mosenthal who had migrated to the United States from Kassel, Germany, in 1853. The beloved elder Mosenthal was a musical composer and conductor of no little fame. He was violinist in the Philharmonic Orchestra and a member of the first chamber-music string quartet in the United States. For many years he served as organist in the Calvary Episcopal Church and was conductor of the famed Mendelssohn Glee Club of New York City. There can be little wonder that his offspring loved the artistic and even made an art of the science of medicine.

Dr. Mosenthal was graduated from Columbia College in 1899 with an A. B. degree. He had his preliminary medical education at the University's College of Physicians and Surgeons, from which he received his Doctorate in Medicine in 1903. He interned in the Medical Division of the New York Hospital (1904-06) and also in the New York Foundling Hospital (1906-07). His subsequent half-century of service to medicine carried many appointments. Between 1908 and 1910, he was Attending Physician at Seton Hospital; during the same period he was Attending Physician to the outpatient department of the New York Hospital.

Dr. Mosenthal's leaning was in the direction of biological chemistry, which in those days was still a young science. Between 1908 and 1914, he was instructor and associate in the Department of Biological Chemistry at Columbia's College of Physicians and Surgeons. In 1910, he became Attending Physician in Diseases of Metabolism at the Vanderbilt Clinic, and Assistant Visiting Physician to the Presbyterian Hospital of New York City. In this period he become closely associated with the famous Janeways, both father and son. In the summer of 1912, he studied under Schleyer in Würtemburg, Germany. Dr. Mosenthal held his New York appointments until 1914, when the Johns Hopkins Medical School lured him to Baltimore as Associate Professor of Medicine with Dr. Theodore Janeway. When Dr. Janeway left for service in the first World War in 1917, Dr. Mosenthal became Acting Professor of Medicine at Johns Hopkins; he held this position until 1918.

In 1919, he returned to his Alma Mater to become an Associate in Medicine, and at the same time started his private practice of medicine. In 1920, he became Professor of Medicine and Chief of the Department of Medicine of the New York Post-graduate Medical School and Hospital; he held these positions until 1935. At the Post-graduate Hospital he established and directed probably the first U.S. metabolic clinic.

Among his other staff positions were appointments as Senior Attending Physician to the Reconstruction Hospital Unit of the New York Post-graduate Medical School and Hospital (1930), Consulting Physician at Sea View Hospital (1931); later, Visiting Physician to the same institution. In 1940, he was made Honorary Consulting Physician to the Hospital's Division of Metabolism. From 1931 to 1946, he was Visiting Physician to the 4th Division of Bellevue Hospital. From 1934 to 1947, he was Clinical Professor of Medicine at Columbia University. From 1946 to 1951, he was Associate Clinical Professor of Medicine at the New York Medical College. At the time of his death, he was Consultant in Medicine at the New York University Hospital, the New York Infirmary, Goshen Hospital, and St. Luke's Hospital in Newburgh, New York.

He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians and of the New York Academy of Medicine. He was a member of the Association of American Physicians, the American Society for Clinical Investigation, the American Gastro-enterological Association, the Society of Experimental Biology and Medicine, and the International Society of Gastro-enterology. He belonged to Nu Sigma Nu Fraternity and to the Century Club.

Dr. Mosenthal had a genius for organization. For several years before the creation of the New York Diabetes Association, he had assiduously and tirelessly

explored many channels to create professional interest in the formation of an association which would foster organized interest in the field of diabetes in the New York area. It was not until 1934, when the late Dr. Charles F. Bolduan of the Department of Health of New York City matched plans with his, that the New York Diabetes Association came into being. Dr. Mosenthal engineered the raising of the necessary funds and contributed the organizational knowledge which made possible the foundation of the Association.

Dr. Mosenthal's horizon extended far beyond the New York area. There had been kindled in him the urge to see an influential national association dedicated to the problems of diabetes, both professional and sociologic. Early in the year 1939, he announced to several of the members of the Board of Directors of the New York Diabetes Association that he was on his way to Cincinnati to talk over with Dr. Cecil Striker and with Dr. William Muhlberg, another patriarch of organized diabetes in this country, the possibility of creating an American diabetes association. He was given the blessing of the New York group with a proviso, to the advantage of which he was keen enough to subscribe, that he would not under any circumstances accept the first presidency of any national organization if or when it were created. It was felt that the national association would obtain its greatest impetus if Dr. Mosenthal were not in the Chair but remained in the ranks to do the actual spade-work. He had long since demonstrated to his friends in the New York area that he was by nature a tenacious worker who had inherited just sufficient Teutonic stick-to-itiveness—at times even exasperating to his confreres—to achieve any goal he might set for himself. With Mosenthal behind the project, it was a foregone conclusion that the very best talent in the country would be enlisted as an organizing group. The quality of the founding body of the American Diabetes Association proved that this confidence had not been misplaced. The Association grew like a weed into one of the few powerful national organizations in the interest of public welfare controlled strictly by physicians. Dr. Mosenthal became the second President of the Association, succeeding Dr. Cecil Striker.

Dr. Mosenthal lived to see the monument he had built in the New York Diabetes Association express its appreciation of his efforts. On November 10, 1953, the Board of Directors made a gesture to implement its gratitude to its organizer by making him Honorary President. In his letter of acceptance, Dr. Mosenthal stated: "It is now forty-seven years since I began to be interested in diabetes—first, under Dr. Theodore Janeway, being retained as his assistant, especially for the treatment of diabetes, at a time when virtually nobody in the country did anything about diabetes. In 1912 I started what, I believe, was the first successful diabetes clinic in the United States, at the Vanderbilt Clinic. In 1915, a similar effort was made by Walter Campbell in Toronto. I imagine it was really the successful launching of clinics that built in the early days the cornerstone of the public health interest which under the constant needling of Charles Bolduan was represented in the creation of the New York Diabetes Association and the American Diabetes Association."

On the passing of Dr. Mosenthal, the Directors of the New York Diabetes Association adopted the following resolutions:

Whereas, Doctor Herman O. Mosenthal departed this life on April 24, 1954, and

Whereas, he fathered the New York Diabetes Association and was, as well, a guiding genius behind the creation of the American Diabetes Association, and

Whereas, Doctor Mosenthal's untiring missionary efforts made possible the growth of both organizations into powerful agencies serving mankind not only in this hemisphere but, by extension of the ideals and principles which he thereby fostered, throughout the world, and

Whereas, he was the first President of the New York Diabetes Association and the second President of the American Diabetes Association, and

Whereas, on November 10th, 1953, in electing him Honorary President of the New York Diabetes Association, the members of this organization sought to express while he still lived the high esteem in which he was held and the Association's gratitude for his many faithful services, and

Whereas, the Board of Directors of the New York Diabetes Association would at this time memorialize and document for the historical knowledge of future Boards the Association's indebtedness to the late Doctor Herman O. Mosenthal,

Therefore, Be it Resolved: that the members of the said Board do express their profound sorrow in the passing of the greatest of the Association's benefactors, and that they do by this instrument gratefully acknowledge for formal inclusion in the archives of this Association the tireless devotion of Doctor Herman O. Mosenthal to the cause of diabetics, present and future, and that they do humbly bespeak the sentiments of all of his erstwhile fellow-members in the Association when they resolve:

"Well done, good and faithful servant!"

Education in Diabetes

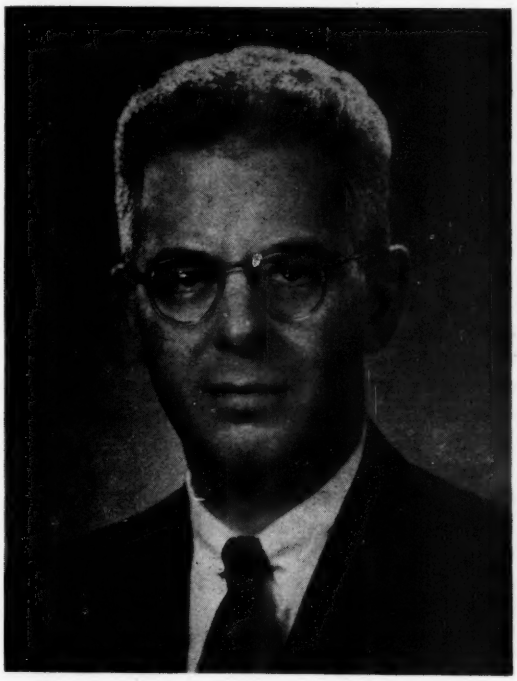
Randall G. Sprague, M.D., Rochester, Minnesota

In this fourteenth year of the American Diabetes Association we are again confronted with the necessity for asking ourselves what we are trying to accomplish in the field of diabetes. Periodic self-examination is always desirable, but at this time the necessity for it is forced upon us by financial problems which confront us. I am sure you realize that not all of the activities of the Association are self-supporting. It is an inescapable truth that the demands which are being made upon us for information and services are increasing beyond our ability to finance them. Our troubles are of our own making, for these demands, I believe, are in no small measure due to the interest in diabetes which we have awakened in the medical profession and in the public. Later I shall discuss some of the ideas of the Council regarding our fiscal problems, but first I should like to present some personal thoughts about how our income and our energies can best be expended in the interest of diabetics.

Our general objective is simple and sound, and is so well-known to all of us that it hardly needs to be recounted: improvement of the welfare of diabetics everywhere. The diabetic patient was the sole reason for the birth of our Association and remains the sole basis for its continued existence and remarkable growth. If we are to make sound and steady progress toward a better life for the diabetic, which of our activities should receive the major emphasis? I presume the retiring president has the privilege and responsibility of presenting his views on such matters. In doing so he must bear in mind, for the future preservation of his own ego, that he is not equipped with a crystal ball which enables him to foresee all of the changes which might take place in the field of diabetes and in the thinking of our Council in the coming years.

THE SCOPE OF EDUCATION IN DIABETES

Of all the manifold endeavors of the Association, those which are included under the heading of education are at this time, in my opinion, the most significant to the welfare of the diabetic patient. In no disease does education play a more important role than in diabetes. I refer to education in a broad sense to include the teaching of diabetes to the medical student, the physician, the diabetic and his family, and the public. An



RANDALL G. SPRAGUE, M.D., PRESIDENT, 1953-54

Dr. Sprague was born in Chicago, September 22, 1906. He attended Northwestern University, receiving the degree of B.S. in 1930, M.S. in 1935 and M.D. in 1935. He received the degree of Ph.D. in Medicine from the University of Minnesota in 1942. After internship at the Presbyterian Hospital in Chicago, 1934-35, Dr. Sprague went to the Mayo Clinic on a Fellowship in Medicine, 1936-39. He became a member of the staff of Mayo Clinic and since 1948 has been Professor of Medicine in the University of Minnesota (Mayo Foundation).

Address of the President delivered at the Banquet, 14th Annual Meeting, San Francisco, Calif., June 19, 1954.

appreciation of the problems of diabetes, which to each of these groups are somewhat different, is more vital to the welfare of the individual diabetic than any other thing. I believe it is not immodest to claim that our Association has played a large part in the dissemination of information about diabetes. The influence of our educational endeavors, sometimes subtle and not readily apparent, is, I am sure, felt to some degree throughout our country, and in a more attenuated form far beyond our national boundaries. At no time in history has there been a more widespread appreciation of the problems of diabetes than now.

PROFESSIONAL EDUCATION

Our activities in professional education have been fairly extensive, but much remains to be done. There is a great fund of knowledge about diabetes which somehow must find its way to the rank and file of medical practitioners, starting at the level of the medical student. The patient depends upon his physician, and if he is to profit from the scientific advances made in recent years it will have to be through his physician. The principal elements in our professional educational activities have been the annual meetings, the annual postgraduate courses, and our journal DIABETES, which includes "Diabetes Abstracts." Who can question the importance of these activities in enabling the interested physician to give something better than pedestrian care to his diabetic patients, yet who can fail to recognize that we still have much to do in the education of physicians?

Let us digress for a moment on the unusual significance of the physician-patient relationship when the patient is a diabetic. Perhaps we do not realize the full extent of the diabetic patient's dependence upon his physician. I think I do, because I developed diabetes 33 years ago, when I was a sophomore in high school. I was fortunate enough to learn the ground rules of diabetes from some physicians who made a profound impression upon me. At that age, or for that matter at any age, the physician's words "you have diabetes" give rise to uncertainty, insecurity and even fear in the mind of the one whose carbohydrate metabolism has gone awry. He suddenly finds himself in a different category of humanity from that of the ordinary individual. At the outset and forever after he needs two kinds of help—enlightened medical care in the purely scientific sense, and a kindly understanding of the human aspects of his problem. He looks to his physician for scientific wisdom, but with this, warmhearted compassion must be so neatly blended and integrated that the patient does not recognize them as separate skills. He knows only that his physician understands his problem in all its aspects, and knows how to counsel him in a kindly and practical way. For the diabetic, the "physician-patient relationship" must be established early, or it may never come into being. To accomplish this, it is apparent that the physician should possess both a large capacity for loving kindness and a full appreciation of the physiologic vagaries of diabetes, gained through educational processes, including experience. His education in diabetes, begun in medical school, must be continued ever after. I do not need to remind you that such education is difficult to achieve. Many medical conditions compete for the attention of the physician. It will be a sad day, however, for the diabetic should our Association diminish its efforts in professional education on this account.

PATIENT EDUCATION

Let us not forget that the end and object of the education of the physician in diabetes is the education of the patient himself. I learned early in my diabetic career that the patient must shift for himself, so to speak, in the day-by-day care of his diabetes. There are many things he must know if he is to keep out of trouble. He must study his disease, learn its pitfalls and at all times be responsible for his personal care. His physician, however faithful a counselor he may be, cannot be always at his side to answer the questions about diabetic care that inevitably arise. To bridge the intervals between visits to his physician, the diabetic must have a sound insight into the ways of coping with the daily problems of diabetes. But no amount of education will sustain the diabetic between visits to the physician if the intervals are too long, for new problems keep arising, morale tends to sag, and bad habits and error creep in. The counsel and inspiration of the physician (as well as a determination of the blood sugar) must be sought at regular intervals.

But let us return to the matter of patient education. It must begin on the day his diabetes is discovered. It must be thorough and inspiring, and it must come from the physician's own store of knowledge of and experience with diabetes. The educational endeavors of our Association must reach patients for the most part through physicians, though we do accomplish much through the FORECAST, the affiliates and other media.

That diabetic know-how is the essential ingredient in successful living with diabetes was well illustrated by the panel of physicians with diabetes which appeared at last year's annual meeting in New York. The men on this panel who related their diabetic stories were physi-

cians who were well schooled in the ways of diabetes, but the same principles of diabetic education apply to others, for the diabetic physician lives under the same physiologic and psychologic laws as the diabetic layman.

PUBLIC EDUCATION

Our efforts in public education have been associated for the most part with case-finding activities carried out through local units of the medical profession. Since diabetes affects an appreciable segment of the population, either directly or indirectly, it is axiomatic that public awareness of the problem is potentially of great value to the individual diabetic. Such awareness is of value in our efforts to find the unknown diabetic so that medical care can be provided early in the course of his disease. In some instances diabetes may be prevented in the blood relatives of diabetics if they learn that avoidance of obesity is important. The opportunities for gainful employment for diabetics can be increased. Proper care for diabetics in emergencies can be enhanced. We have all heard of diabetics who have been cast into jail in the midst of an insulin reaction, to languish there until physiologic processes brought about recovery from a stupor which was mistakenly thought to be alcoholic. We have also heard of death attributed to forceful withdrawal of insulin on the grounds that the police suspected opiate addiction. Perhaps the police force should be a special object of our educational work! In an emergency of a grander scale, such as might result from sudden exposure of a large population to atomic irradiation from abroad, would not a public awareness of the special hazards to the diabetic be of great importance? Lastly, public interest in diabetes is important in promoting research. Who can deny that such public interest, shaped in part by the activities of our Association, helped to stimulate the establishment of the National Institute of Arthritis and Metabolic Diseases, where diabetes is the principal metabolic disease under study and whose financial grants support much of the research now undertaken in many universities?

Likewise, public awareness of diabetes can be expected to increase support for the research activities of our own Association.

I cannot escape the conclusion stated at the outset of this discussion, that the greatest future of our Association lies in the field of diabetic education. Education will stimulate research, for the instinct to inquire about diabetes depends upon some acquaintance with the problems posed by the disease. With the limited funds now at our disposal, our monetary support of research must necessarily be limited.

We do what we can, but to my mind, our educational activities are the ones in which we have made and will continue for a long time to make the most significant contributions.

It would be advantageous to have much larger funds with which to stimulate and support research in diabetes. However, for a variety of reasons which need not be detailed here, our Council has expressed itself against becoming a voluntary health agency engaged in public fund raising. Rather than turning to the general public for support, it seems more fitting to limit our appeals to the beneficiaries of our endeavors, the diabetics themselves and their families. In so doing, we must not fall into the error of some organizations which have permitted fund raising to become an end in itself, nor must we delude ourselves that money will do things that it will not do. These mistakes we want to avoid. The position of dignity and respect which our Association has won in the eyes of the medical profession and the public must not be undermined by avarice. Claude Bernard once said that the liver is not diseased in diabetes, but that it "sins through exuberant vitality." We are exuberantly vital, but let us not in our exuberance be likened to the liver of the diabetic, which in a lawless manner produces an extravagant amount of sugar of little benefit to the patient.

The Annual Meeting, June 19-20

THE SCIENTIFIC SESSIONS

The Program, which was described in a previous issue of DIABETES, attracted a large audience. Clinical and experimental papers were subjects of keen attention. A particular highlight of the Sessions was the panel discussion, "Diabetes and Pregnancy," with Garfield G. Duncan, M.D., as moderator and M. Edward Davis, M.D., Lester J. Palmer, M.D., E. Stewart Taylor, M.D., and Priscilla White, M.D., participating. The Banting Memorial Lecture delivered by Sir Henry Hallett Dale, to be printed in a coming issue of DIABETES, was enthusiastically received.

BUSINESS MEETING

The Annual Business Meeting of the Association was held June 20. The report of Randall G. Sprague, M.D., President, was followed by reports of the Secretary, Treasurer, Executive Director, Nominating Committee, and Committee on Finance.

Report of the President

The Association continues in a healthy condition, and its several programs are going forward in a generally satisfactory manner. At this time I should like to comment on two happenings of the past year.

Within the year we have lost by death three distinguished physicians who played unusually important roles in the founding and development of the American Diabetes Association. These are Dr. Joseph H. Barach, of Pittsburgh; Dr. Herman O. Mosenthal, of New York; and Dr. Rollin T. Woodyatt, of Chicago. By their deaths, the Association, their patients and the medical profession as a whole have suffered a great loss.

Dr. Joseph H. Barach was one of the founders of the Association, and he served as its fourth President. He was the Presiding Officer at the Annual Meeting in Toronto in 1946, on the occasion of the celebration of the twenty-fifth anniversary of the discovery of insulin. He conceived the idea of the Banting Medal and, indeed, actually provided the medal.

Dr. Herman O. Mosenthal was one of the most active moving spirits in the founding of the Association, and he gave tirelessly of his energies in the early planning of the Association's activities. He was its second President, and continued to manifest a vital interest in the affairs of the Association virtually until the time of his death a few months ago.

Dr. Rollin T. Woodyatt was a Member of the Council at the time of the founding of the Association, and served on the Council for six years. In 1948 he delivered the Banting Memorial Lecture at the Annual Meeting in Chicago. He made notable contributions to knowledge about diabetes in the experimental laboratory, in the care of patients and in the teaching of students and physicians.

It is gratifying to be able to report to you that the Committee on Membership and the Council have voted that Drs. Barach, Mosenthal and Woodyatt be elected to Honorary Membership in the Association posthumously.

I should like next to report that last September the Association was invited to participate in public hearings before the House Committee on Interstate and Foreign Commerce in Washington. The chairman of this committee is Representative Charles A. Wolverton, of New Jersey. The subject of the hearings was "The Causes, Control and Remedies of the Principal Diseases of Mankind." The invitation was received on short notice. After the opinion of the Executive Committee had been obtained as to the Association's participation in the hearings, very little time remained for preparation of formal statements. However, statements were prepared through the efforts of Drs. John A. Reed and Howard F. Root, Mr. Herbert H. Marks, Mr. J. Richard Connelly and myself. The hearing on diabetes was held on October 7, 1953, with Dr. Reed, Mr. Connelly and myself representing the Association. Additional participants were Dr. Arnold B. Kurlander, Assistant Chief, Division of Chronic Disease and Tuberculosis, United States Public Health Service, and Dr. Hugh L. C. Wilkerson, Chief, Diabetes Section, Division of Chronic Disease and Tuberculosis, United States Public Health Service.

The representatives of the Association presented statements on the general problem of diabetes and on the program and activities of the Association in the field of diabetes. At the conclusion of our statements, Congressman John W. Heselton (Massachusetts) stated that he wished to ask in a spirit of friendliness why the American Diabetes Association is not devoting more of its funds to the support of research on diabetes. In anticipation of this question, a statement of the objectives, activities and various programs of the Association had been prepared by Mr. Connelly and was presented. At the conclusion of Mr. Connelly's statement, the chairman of the Committee said, "Mr. Connelly, I think the Association for whom you have spoken is entitled to a great deal of credit. I think that is one of the most comprehensive programs that has been presented to us by any organization. When I realize that you are doing it as a private organization, you might say, with no public appeal for funds, I am astounded that you could have such an expansive and expanding program as you have indicated. I think you are to be highly commended for the evident worthwhile work that is being done by your Association."

RANDALL G. SPRAGUE, M.D.

Report of the Secretary

My report will be condensed in the interest of time.

Your Association engages primarly in education which is divided into three portions: Professional education of which this meeting is a part; patient education, and public education and case finding. Those of you who have engaged in any medical society endeavor, be it on

a city, local, county or state or national level, know of the necessity and properness of good administrative mechanics behind all of a society's projection of purposes.

May I assure you as the Secretary of this Association that this is so with your American Diabetes Association.

I made trips to the national office in New York City to review from time to time the administrative setup. I have only recently done so since the removal of the offices to their new quarters at 1 East 45th Street, New York City.

I wish to report good departmentalization of the office with most competent assistance.

I wish to take this opportunity to extend to Mr. Connelly, our Executive Director, on the part of the officers and the Council, and I know the membership, our sincerest appreciation of his value and worth to our organization and to thank him for his untiring administrative help to all of us, and to pass on to his staff in New York likewise this appreciation.

As an ex officio member of all committees of your Association, it has been my obligation to attend the meetings of the committees from time to time. I know here again the entire membership will join me in expressing thanks to the chairmen and all the members of these committees for their magnificent endeavors and fruitful production.

In short, in the fulfillment of the many endeavors of your Association, the mechanics of administration and staff is excellently geared to the performance of these functions.

JOHN A. REED, M.D.

Report of the Treasurer

Since there is not much time at this Business Meeting this report of necessity must be brief. Any Active Member of the Association who may desire to study the Financial Statement for the last fiscal year may receive a copy by writing to the National Office.

I am pleased to report to you that the Association is within its budget for the past fiscal year. It is also a pleasure to report that our Executive Director has been able to set aside year by year funds to make up a reserve. Our Association should have such a financial backlog in case of a national emergency.

Approximately one-half of our income is earned by the Association. This comes from membership dues, subscriptions to the ADA FORECAST, our journal DIABETES, and other self-financing projects and interest on savings. The balance of our income is received as gifts and grants from corporations who generously support our activities. The corporate contributors are as follows:

Abbott Laboratories
Ames Company, Inc.
Armour Laboratories
Becton, Dickinson and Company
Burroughs Wellcome & Co., Inc.
The Chicago Dietetic Supply House
The Denver Chemical Mfg. Co., Inc.
Eli Lilly and Company
Monsanto Chemical Company
E. R. Squibb and Sons
The Union Central Life Insurance Company

On behalf of the American Diabetes Association, I wish to take this opportunity of expressing our deep gratitude and sincere appreciation to these corporations for their loyal support.

Your Council is aware of the necessity of increasing our income to meet the future needs of the Association. It is also aware of the financial needs of our Affiliate Associations. In the report of the Committee on Finance, as accepted by the Council, recommendations are set forth to meet this situation. Time does not permit presenting them in full at this time, but the recommendations can be summarized as follows:

First, the Council believes that fund raising should be limited to diabetics, their families and friends, and not be carried to the general public.

Secondly, the Council recognizes the financial needs of its Affiliates and pledges to do its part in such a limited campaign. It expects the Affiliates in turn to recognize the financial needs of the Association and to give generously to the work of the national Association.

To put the plan in just a few words, the national Association will join with its Affiliates in a financial campaign which will be conducted among diabetics. The Council believes that a financial campaign characterized by truthfulness, moderation and dignity, can be successful and result in a sounder financial condition of the Affiliate Associations on the one hand and the national Association on the other.

WILLIAM H. OLMSTED, M.D.

Report of the Executive Director

It is a real pleasure to greet the membership once again, an occasion, however, that happens only too infrequently.

This is unfortunately one of the inherent limitations of a national organization. Even in a meeting such as this we are all very busy, and there is little opportunity to do more than just greet each other in the hall.

I want to thank Dr. Reed for the very kind and thoughtful words. However, any progress that is made

in administration is due to the co-operation which we receive from the Secretary, the President and the officers and Councilors and the entire membership of the Association. Also, I think Dr. Sprague is being very modest. Dr. Sprague, serving as chairman of the group for the Wolverton Committee, the House Committee on Interstate and Foreign Commerce, presented a brilliant statement to them. Dr. Reed also presented a statement that was equally worth-while.

We are in very good shape administratively. However, I do have an apology, an explanation to the membership relative to the Membership Directory. This has been delayed due to a complete reorganization of our membership records. We hope to have the directory in the mail this summer. We have an August deadline. We hope to make it. The directory in addition to an alphabetical and geographical list of members will include a new Constitution and Bylaws of the Association, a list of all Honorary Members and all past officers and Councilors.

As I am sure most of you know, our affiliate service program is in full swing. Mr. S. Ross Pond is serving as Field Representative. If any of you are interested in organizing an affiliate association in your area, if you will get in touch with Mr. Pond or me, we will be glad to help you.

Probably one of the administrative highlights of the year is the new office which Dr. Reed referred to. We hope that all the members will feel free to drop by and visit us.

An item which appeared in one of the national magazines might be of interest to you. You probably saw it in *Newsweek,* and we would like to report at this time that *Newsweek* has been contacted relative to the item which appeared in the May 25 issue about an alleged substitute for insulin. No satisfactory information was secured. Further, the matter was investigated with other reliable sources, and they had no information about the alleged product.

Once again I would like to thank the membership for its cooperation and invite you all to drop by and see us at the new office.

J. RICHARD CONNELLY

Report of the Nominating Committee

Before presenting this report, I wish to state the requirements of the Constitution and Bylaws concerning the composition of this Committee. The Nominating Committee is made up of the three most recent past Presidents. The individual who is the senior in point of service as past President and who is present at the meeting shall be Chairman. If any of the three past Presidents are not present at a meeting, it is the privilege of the Chairman to select a past President who is present to fill the vacancy. The nominations of this Committee are submitted to the Council for approval, and are then in turn submitted to the membership at the Annual Meeting.

In connection with this particular Committee, I would like to say that Dr. Arthur R. Colwell of Chicago, who is the second member on the Committee, was prevented for personal reasons from being here. As provided in the Constitution and Bylaws, the Chairman selected a past President present at the meeting to fill his place, and in that place Dr. Howard F. Root of Boston served.

The duties of the Nominating Committee, as I am sure you all realize, are becoming increasingly difficult because of the very large number of highly qualified men, men qualified not only from the standpoint of ability and of what they have contributed to the field of diabetes, but from the standpoint of service, and I would like to emphasize service. Holding to these principles and considerations, we prepared a slate for the Council. The Council has approved this slate of candidates and I will now read them to you.

For the three-year term on the Council expiring 1957:

Dr. Garfield G. Duncan of Philadelphia
Dr. Edwin L. Rippy of Dallas
Dr. E. Perry McCullagh of Cleveland
Dr. Herbert Pollack of New York City
Dr. Franklin B. Peck, Sr., of Indianapolis
Dr. Blair Holcomb of Portland, Oregon

To complete the unexpired term expiring in 1955, created by the death of Dr. Joseph H. Barach:

Dr. Joseph T. Beardwood, Jr., of Philadelphia

To complete the unexpired term expiring in 1955, created by the resignation of Dr. Peter H. Forsham:

Dr. Forsham has served two years of a three-year term on the Council and finds that his obligations prevent him from being of such service as he would hope to give this organization. He asked me to present to the Council his resignation and expressed the hope that he would be requested to give service to our Association at a later date, when he has fewer obligations with The Endocrine Society.

Therefore, to fill that unexpired term:

Dr. Thomas P. Sharkey of Dayton, Ohio

is nominated.

Then, because the nomination for Second Vice President creates a vacancy on the Council, to complete the unexpired term expiring in 1956 the name of:

Dr. Francis D. W. Lukens of Philadelphia is presented.

Now for the officers:

President: Dr. Henry B. Mulholland of Charlottesville, Virginia

First Vice President: Dr. Henry T. Ricketts of Chicago

Second Vice President: Dr. Frederick W. Williams of New York City

Secretary: Dr. John A. Reed of Washington, D. C.

Treasurer: Dr. William H. Olmsted of St. Louis

It was moved and seconded that the nominations be closed and the nominees included in the report of the Nominating Committee were duly elected.

LESTER J. PALMER, M.D., *Chairman*
FRANK N. ALLAN, M.D.
HOWARD F. ROOT, M.D.

*Report of the Committee on Finance**

Your Committee believes a medical organization such as ours, interested in patient and public education, has as its first function the construction of its programs. Its efforts should be concerned with working out programs which are needed and have proven to be workable and effective. There must be conviction in the minds of those responsible for the programs that they have been effective and should be expanded as needs arise. The emphasis, therefore, is on programs, and fund raising is a secondary but necessary matter. When the organization finds that its programs will need more money for support, the question arises how *much* money will be needed. It is obvious that the cost of the program must have the same meticulous study that has been applied to the study of the programs themselves. We believe it is only honest to state publicly the estimated cost of the programs. This means that if fund raising is attempted, a definite goal should be set.

If any sort of fund raising is undertaken, then we must recognize that there are various ways of appealing to the public as a whole, or to any section of it. Disregarding what we personally believe to be wrong methods, let us consider the principles underlying good methods of fund raising. Our Community Chests might be taken as an example. Community Chests are a personal, man to man, appeal for a group of causes which a Committee of citizens has thoroughly investigated, and which they recommend to the public as being worthy in all respects of their support. The workers who raise the money know the cause to be worthwhile. The publicity is, we believe, characterized by honesty, straightforwardness and dignity. In most cities the public is invited to inspect the agencies that make up the Community Chest throughout the year. Everyone may know how the money is spent. When the ADA goes into fund raising, basing such a financial campaign on the diabetics themselves, we have many fine examples of how to conduct ourselves in an honest and dignified manner.

To sum up: The philosophy we propose the American Diabetes Association to follow can be characterized as follows: (1) thorough study of program from standpoint of need and effectiveness; (2) just as thorough study of the cost of such a program with proof that the amount asked for is conservative; (3) campaign methods that are honest, straightforward and dignified.

Study of our Financial Program Needed

First, let us call your attention to the fact that we have been asking and getting approximately $100,000.00 per year as gifts. This money, coming as it does from so few large givers, is insecure. But, in addition, it is questionable in our minds whether this above sum will meet the needs for anticipated expansion. Although we may expect Affiliates to raise the money for their own budgets, the expansion of the Affiliate Program means increased expense in the national office. We must give the Affiliates increased service and help with their programs. We will receive from them financial support as we in turn give them service. But all this means a steady expansion of the national office and substantial increase in cost of operation.

Furthermore, there are plans for expanding the programs on Professional Education, Patient Education, Public Education and Case Finding. The Committee on Research has asked for funds, amounting to $50,000.00 per year, starting immediately. All Committees need to study their programs and the financial needs, now, and as of the future.

Altogether the financial picture of the near future can be summed up as a need for increased funds. Just how much must depend on immediate studies by this Committee with the help of the various Committees concerned.

The Present Situation

In a series of recommendations passed at the January 16-17, 1954 meeting, the Council has outlined the principles involved in fund raising, and asked this Committee to come to the Council with definite plans based on these principles. At that time the Council adopted the following recommendations, which the Committee on Finance now reaffirms:

*Presented to the Council at the 14th Annual Meeting.

Recommendation No. 1. "It is recommended that the Council of the American Diabetes Association approve the principle that diabetics, their families and friends, be asked to contribute to the financial support of the organization; further, that the Council reaffirm the Association's policy of not engaging in a general public fund-raising program."

Recommendation No. 2. "It is recommended that the American Diabetes Association organize an annual fund-raising campaign which shall be based in part on the participation of the Affiliate Associations. It is also recommended that Affiliates be urged to participate in such a campaign, and contribute generously to the General Fund and the Clinical and Research Fund of the American Diabetes Association."

Recommendation No. 3. "It is recommended that the following principles be accepted as a guide to the degree of participation of the American Diabetes Association, on the one hand, and the Affiliates on the other, in fund-raising campaigns. The national organization shall furnish information on the methods of conducting fund-raising campaigns and materials for use in these campaigns, and shall provide such publicity as is consistent with Recommendation No. 1. The Affiliate shall conduct the local campaign and shall provide workers and a field organization for this purpose."

Recommendation No. 4. "It is recommended that, since many thousands of diabetics are not included in the membership of Affiliates, the American Diabetes Association ask these diabetics to contribute to the nearest Affiliate or directly to the national organization, which in turn will give proper credit of any donations to the Affiliate, if one exists in that area."

Reorganization of the Committee on Finance

To gain support of the financial policies which we have adopted, all Affiliates and individuals must be informed. Furthermore, they must be convinced they have a voice in creating financial policy—we must hold their good will. It is our proposal that the Committee on Finance be composed of Affiliate representatives, Governors, and others the President may select. The question of whether this large Committee on Finance should include laymen was discussed at length by the Executive Committee on June 16. The conclusion reached was that at this time laymen should not be included, but that the question may be reconsidered at a later date.

Such a large Committee is unwieldly and ineffectual unless provided with excellent leadership. Therefore, we propose that the President appoint an executive committee of this large group, consisting of the chairman and four vice-chairmen. At least three of these five shall be members of the Council.

The duties of this executive committee shall be to suggest policies to the whole Committee and, secondly, to keep all members informed.

Participation of the National Office in the Financial Program

Such a financial program as we have in mind, and such an expansion of the Committee on Finance as we have proposed, will require additional personnel in the national office. We believe that such additions to the staff should include one individual who has, in addition to other qualifications, some experience in fund raising.

There is plenty of work to keep such personnel busy throughout the year. For instance:

a. A campaign manual is needed for the use of Affiliates in raising money, to set forth the financial philosophy of our Association and to guide them in the organization of campaigns.
b. There is need for a study of the philanthropic policies of industrial concerns such as food manufacturers, pharmaceutical houses, insurance companies, etc., which might be interested in our programs.
c. Foundations should be similarly studied.
d. Letters to members and to diabetics, and editorials and appeals in FORECAST and DIABETES, need to be written, periodically.
e. Other activities outlined in Recommendation 6, as passed by the Council January 16-17, 1954, should be undertaken.

In view of the foregoing considerations it is the opinion of the present Committee on Finance that an amendment to the Bylaws providing for an enlarged Committee on Finance, along the lines suggested above, should be adopted.

In the meantime, it is our opinion that additional personnel concerned primarily with the financial needs of the Association should be employed. I, therefore, move that the Executive Director be authorized by the Council to employ necessary additional staff, one of whom should have, in addition to other qualifications, some experience in fund raising.

THOMAS P. SHARKEY, M.D.,
Chairman
WILLIAM H. OLMSTED, M.D.,
Vice Chairman (Acting Chairman)
ARTHUR R. COLWELL, M.D.
HOWARD F. ROOT, M.D.
CECIL STRIKER, M.D.
JOHN H. WARVEL, M.D.

THE BANQUET SESSION

The Banquet was both a sociable and a serious occasion. Sir Henry Hallett Dale spoke informally on early memories of the discovery and development of insulin with which he was intimately concerned in Toronto and England. He was introduced by Randall G. Sprague, M.D., who presented him with the Banting Medal in behalf of the American Diabetes Association.*

PRESENTATION OF THE BANTING MEDAL TO SIR HENRY HALLETT DALE BY DR. RANDALL G. SPRAGUE, PRESIDENT, AMERICAN DIABETES ASSOCIATION

Sir Henry Dale has come to our country, accompanied by Lady Dale, for the dual purpose of seeing some of the beauties of the western part of the United States and delivering the Banting Memorial Lecture before us today. Sir Henry, we are honored to have you and Lady Dale with us, and we consider ourselves highly privileged to have heard your lecture.

In introducing Sir Henry, I might list the many fields of research in which he has been an active participant or a moving spirit, or both, and the many honors that have come to him. Instead, let me simply say that he is one of the most distinguished and honored men of science of our time. Trained in physiology, he has been an active contributor to medical science throughout the entire modern period of its rapid development; that is, since the turn of the century.

A short time ago, when Sir Henry was in Rochester, Minnesota, on his way westward, he remarked that, when he took his clinical training, scarcely any therapeutic agents available were directed specifically at the cause of a disease; virtually all of the medicines of that day were for alleviation of symptoms. When he entered the clinical wards at St. Bart's, his professor of medicine singled him out, saying, "I am told that you spent two extra years at Cambridge in physiologic research." Sir Henry admitted that he had. "Well, young man," said Professor Gee, "when you enter my wards, leave your physiology behind you. There is no place for it here. What I am teaching is an empirical craft into which science has not yet penetrated."

Such was the state of clinical medicine when Sir Henry decided to devote his life to research in medicine. He worked under Professor Starling at University College, London, and subsequently became Director of the Wellcome Physiological Research Laboratories. In 1928 he became director of the National Institute for Medical Research at Hampstead, a position which he held until 1942. In 1936 he shared the Nobel Prize for Medicine. Since 1936 he has been chairman of the Wellcome Trust of London. During the war years, most of which followed his retirement from the directorship of the National Institute for Medical Research, he was preoccupied with the scientific aspects of England's war effort, and had little time for pursuit of the lines of research which previously had been his greatest interest. Parenthetically, I asked Sir Henry what he thought about retirement, and he responded with great vigor, "It's a bad thing—they work you harder than ever before, and pay you less."

Without even mentioning many of the important positions he has held and researches for which he has been responsible, it is apparent that Sir Henry has contributed greatly to medical science. Not the least of his contributions have been based on his qualities of leadership, inspiration and sincerity in all he undertakes. He has stimulated young men with whom he has been associated to do their finest work. And so his mark in medical science will not be just that of one man, but that of his great self and his many pupils.

Sir Henry, it is the pleasure and honor of the American Diabetes Association to present you with the Banting Medal in recognition of your great contributions to medical science.

PRESENTATION OF THE BANTING MEDAL TO DR. RANDALL G. SPRAGUE, BY DR. FRANK N. ALLAN, PAST PRESIDENT, AMERICAN DIABETES ASSOCIATION

It has been traditional that the man who has most recently retired from the scene of presidential office returns from the wings at the next Annual Meeting to perform a final duty. He is given the opportunity of rendering to his successor, the president then in office, a tribute in recognition of his services.

This year mention should be made of more than leadership in organizational activities, more than achievement in medical science. Attention should be directed to a successful career in which diabetes has not been a handicap. The public knowledge of this example serves as an inspiration to young diabetics and also helps them to receive acceptance in their own fields of activity.

It is most fitting that a man who owes his existence to Banting's discovery should receive as one reward for a successful life, the Banting Medal of the American Diabetes Association.

*Sir Henry's speech, "The Changing Outlook in Medicine," will be published in the September-October issue of DIABETES.

Randy, it gives me personal pleasure to present to you on behalf of the American Diabetes Association this Banting Medal on which is inscribed "Presented to Randall G. Sprague, M.D., for distinguished service to doctor and patient."

MEETING OF THE BOARD OF GOVERNORS

Meeting for the first time, the newly-constituted Board of Governors of the American Diabetes Association began its work in San Francisco on June 18, 1954, by organizing and electing officers for the coming year. A joint session of the Board of Governors and the Council of ADA was held.

Louis K. Alpert, M.D., of Washington, D.C., was elected Chairman of the Board, with Edwin W. Gates, M.D., of Niagara Falls, N.Y., Vice-chairman. Henry E. Oppenheimer, M.D., of St. Louis, Mo., was elected Secretary of the group. As Chairman, Dr. Alpert will serve ex officio as a member of the Council of ADA.

Following the joint meeting, the Board of Governors heard its new Chairman outline its functions, emphasizing that the Governors are to serve as liaison between ADA and the local diabetes organizations and County and State Medical Societies. Policies and programs of the national organization will be interpreted to local groups; local interests and needs will in turn be reflected to the Council by the Board of Governors.

MEETING OF THE ASSEMBLY OF DELEGATES

Delegates of Affiliate Diabetes Associations throughout the country met as the Assembly of Delegates in San Francisco on June 18, 1954, having met the two previous years as the First and Second Conferences of Delegates of Affiliate Associations. Due to travel distances involved, a relatively small number of Affiliates was represented by either Clinical or Lay Delegates, although the Governors attended as Senior Delegates.

Dr. Henry T. Ricketts of Chicago, Second Vice-President of ADA, serving as Chairman of the Assembly, characterized the initial meeting of the new Assembly as one of orientation, with the formal organization of the Assembly scheduled to take place at the Fifteenth Annual Meeting of ADA in Atlantic City in June, 1955. Dr. Ricketts also announced that the Field Representative, Mr. S. Ross Pond, had made field visits to all the Affiliates during the previous twelve months, as well as having visited a number of cities where groups were interested in the formation of new Diabetes Associations.

Problems of membership, programing and educational activities were discussed by the Delegates. A considerable interest was expressed in the 1955 Assembly, with indications that Affiliates had already begun to plan for full representation there by their Delegates.

1954 Detection and Education Program

Over the United States, Committees on Diabetes of State and County Medical Societies and Affiliate Associations of the American Diabetes Association are getting ready for the annual observance of Diabetes Week which is the third week in November—November 14-20—this year.

Many of the readers of this journal—physicians who have displayed an active interest in diabetes and its control as a major health problem—are enthusiastically engaged in these preparations. The American Diabetes Association welcomes that cooperation of its members and other physicians. Without it, the work of public education with regard to diabetes, which is a basic part of the Association's program, would be difficult if not impossible of accomplishment.

As in past years, facilities for mass testing in the Diabetes Detection Drive are a primary part of the educational approach. A thoroughly planned program under competent medical supervision has been worked out. Local committees are being provided with detailed suggestions, based on past years' experience, for the organization of the campaign in their communities, and with a variety of printed matter to help them spread the message of early detection and adequate medical care. Nationally and locally those points will be stressed also in publicity through the press and other media of public information.

This year's will be the seventh annual observance of Diabetes Week. Last year the national Association received reports on 350,000 persons tested. It is estimated that actually over one million were screened and perhaps upwards of two million. The reported screenings are a gain of nearly 50,000 over the previous year and it is hoped that this year will bring a still further increase.

The St. Louis Dreypak was used as a pilot study last year and is to be employed this year on a far larger

scale. Experience has proved it to be a convenient and easily handled method of collecting specimens for urinalysis in wholesale screening tests (see January-February 1953 issue of DIABETES). The Association has made available without charge up to 1500 Dreypaks to each Committee for local experimentation. Orders for larger quantities will be supplied to Committees for authorized programs at a nominal price.

The Diabetes Detection Drive in past years has been the means of guiding thousands of hitherto undetected diabetics to medical care that will enable them to live practically normal lives. That accomplishment stands to the credit of the many public-spirited physicians throughout the country who have given unselfishly of their time and knowledge to bring it about. Every doctor who has participated can feel that it has been a worth-while job, well done.

LOUIS K. ALPERT, M.D., *Chairman*
Committee on Detection and Education

Third Postgraduate Course January 19-21, 1955

As announced in the May-June issue of DIABETES, the Third Postgraduate Course of the American Diabetes Association will be held in Philadelphia, Pa., January 19-21, 1955.

The Course, devoted to diabetes and basic metabolic problems, will be directed by Edward L. Bortz, M.D. General subjects, scheduled for a half-day each, and their respective Chairmen, are as follows: "Normal Metabolism," Charles H. Best, M.D., Toronto; "The Pathological Physiology of Diabetes," Henry T. Ricketts, M.D., Chicago; "The Young Diabetic," A. Lawrence Chute, M.D., Toronto; "Obesity," Frank N. Allan, M.D., Boston; "The Status of Complications," Howard F. Root, M.D., Boston.

For the first time in the Postgraduate series, the program will be highlighted by demonstration of patients in each afternoon session. Each clinic will have a Chairman, Historian and Clinician.

The sessions will be held at the new Lankenau Hospital. The Bellevue-Stratford Hotel will serve as Association headquarters.

A dinner and social hour will be held Thursday evening, January 20.

The registration fee for the three-day course is: $40 for members, $75 for nonmembers. Applications for registration should be sent to J. Richard Connelly, Executive Director, at the National Office.

The Program will be published in DIABETES and Preliminary Programs will be sent directly to all the members.

New Award Added To Annual Medical Student and Intern Essay Contest

An additional award of a $50 cash prize for the best review article or case report has been added to this annual competition sponsored by the American Diabetes Association.

The prize of $250 for the best paper reporting original studies will be continued.

Candidates for either prize may select any subject relating to diabetes and basic metabolic problems. Manuscripts should be submitted by April 1, 1955, to the Editorial Office of DIABETES: *The Journal of the American Diabetes Association,* 1 East 45th Street, New York 17, N. Y.

The prize of $250 for the best paper or original study is again made possible by the generosity of the St. Louis Diabetes Association and the $50 award has been given anonymously by a member of the Association.

The winner and those receiving honorable mention for the 1954 contest will be announced in the next issue of DIABETES.

The Fifteenth Annual Meeting

The next Annual Meeting of the American Diabetes Association will be held in Atlantic City, June 4-5, 1955. As in the past, our meeting immediately precedes the annual session, June 6-10, of the American Medical Association.

Chalfonte-Haddon Hall will again serve as headquarters for our Association. Although there is no guarantee that all of our members can be housed in the headquarters hotel, every effort will be made to do so. Reservation cards will go forward to the members in the near future.

Physicians and other scientists are invited by Frederick W. Williams, M.D., Chairman of the Association's Committee on Scientific Programs, to submit abstracts of papers which they would like to present at the Scientific Sessions.

Persons interested are requested to submit eight copies of the abstracts to facilitate review of their material by the Committee.

Second Congress of the International Diabetes Federation

The Second Congress of the International Diabetes Federation, as announced in the May-June issue of DIABETES, will be held in Cambridge, England, July 4-8, 1955. Sir Lionel Whitby, K.V.O., M.C., Master of Downing College, Cambridge, will be Honorary President. The Diabetic Association (Great Britain), 152 Harley Street, London, W 1, will act as host. Information about reservations and so forth may be secured from Mr. James G. L. Jackson, of that Association, or from Dr. F. Gerritzen, Secretary-Treasurer, International Diabetes Federation, 33 Prinsegracht, The Hague, Netherlands. Copies of the program may be secured from the National Office of the American Diabetes Association as soon as they become available.

New Members

The following Active Members were elected as of July 1 and August 1, 1954:

California
- Embick, James F. — Richmond
- Murray, John F. — Fresno

Colorado
- Livingston, Wallace H. — Denver

Connecticut
- Tracy, Frederick E. — Middletown

Illinois
- Paynter, Camen R. — Chicago
- Sondag, Roger F. — Murphysboro

Indiana
- Havens, Oscar D. — Cicero
- Thornburg, Kenneth E. — Indianapolis

Michigan
- Jarsen, Frank J. — Detroit
- Kuipers, Siebe W. — Holland

Minnesota
- Chapin, Lemuel E. — Rochester
- Miller, William J. — Rochester
- Shea, Andrew W. — Minneapolis

Missouri
- Ide, Lucien W. — St. Joseph

New York
- Kosmaler, Charles H. — Elmira
- Leifer, Edgar — New York
- Stonehill, Sydney — Rochester
- Verdeschi, Felix L. — Ozone Park
- Weiss, Harry — New York

North Carolina
- Tidler, James — Wilmington

North Dakota
- Hochhauser, Martin — Garrison

Ohio
- Bloodworth, James M., Jr. — Columbus
- Mesaros, Laura K. — Steubenville

Oklahoma
- Howard, Robert P. — Oklahoma City

Pennsylvania
- Bloom, Charles H. — Altoona
- Crystal, Harry — Reading
- McKinney, William L. — Reading
- McShane, James R. — Reading
- Rettew, Philip L. — Reading
- Reuting, Ruth E. — Titusville
- Sherk, Carl R. — Lebanon

Tennessee
- Webster, Burnice H. — Nashville

Texas
- Coleman, James A., Jr. — Temple
- Reppert, Lawrence B. — San Antonio

Virginia
- Bray, Maurice M. — Suffolk

Wisconsin
- Weisberg, Joseph H. — Superior

OTHER COUNTRIES

Australia
- Harrison, Keith S. — Sydney

Canada
- Guravich, Judah L. — Lancaster, N. B.
- Savignac, Bernard — Sorel, Que.

Hawaii
- Togasaki, Teru — Honolulu

The following Associate Member was elected as of July 1, 1954:
- Adler, Helen R. — Rye, N. Y.

News of Affiliate Associations

With the granting of Affiliate status to three Diabetes Associations by the Council of the American Diabetes Association at its Annual Meeting in San Francisco on June 18, the number of local Affiliate Associations of the American Diabetes Association rose to 37.

These newest Affiliates are the Fresno County (California), Colorado and West Virginia Diabetes Associations. The Fresno Affiliate has a Clinical Society and a Lay Society. The Colorado group has organized a representative Clinical Society and is considering the formation of component Lay Societies, possibly in Denver and in Colorado Springs. The West Virginia Affiliate has a state-wide Clinical Society and a Lay Society in Charleston. Current officers and committee chairmen are included in the following news reports.

The COLORADO DIABETES ASSOCIATION'S officers' slate consists of the following: George Curfman, M.D., President; Richard Cullen, M.D., Vice-President; Robert F. Berris, M.D., Secretary-Treasurer. Willis L. Bennett, M.D., is Chairman of Membership Committee. The officers of the state-wide association will also serve the Clinical Society.

The DIABETES ASSOCIATION OF ATLANTA elected the following officers in May: L. Harvey Hamff, M.D., President; Charles Raymond Arp, M.D., Vice-President; Harold A. Ferris, M.D., Secretary-Treasurer. Lester Petrie, M.D., is Chairman, Committee on Detection and Education. Clinical Society officers for 1954 are: L. Harvey Hamff, M.D., President; C. Raymond Arp, M.D., Vice-President; Harold A. Ferris, M.D., Secretary-Treasurer.

The DIABETES ASSOCIATION OF GREATER CLEVELAND named these officers in January: Joseph I. Goodman, M.D., President; Mrs. Earl R. Hoover, Vice-President; Mrs. Rodney Sutton, Secretary; Mr. Sam Benjamin, Treasurer. Paul Wisenbaugh, M.D., is Chairman of the Committee on Detection and Education. The Clinical Society officers for 1954 are: M. Irving Sparks, M.D., President; Penn G. Skillern, M.D., Vice-President; Samuel Spector, M.D., Secretary.

The FRESNO COUNTY DIABETES ASSOCIATION'S new officers, elected in June, are: Leo Goodman, M.D., President; Max Millar, M.D., 1st Vice-President; Mrs. Katherine Pavlovich, 2nd Vice-President; Mr. William Forbes, Secretary; Mrs. Katherine Spencer, Treasurer. The following Chairmen were appointed: Robert Monlux, M.D., Committee on Detection and Education; James L. Caffee, M.D., Committee on Camps. The Clinical Society officers are: Max Millar, M.D., President; I. G. Tillotson, M.D., Vice-President; Mrs. Katherine Pavlovich, Secretary; Alfrieda Sherman, Treasurer. The Chairmen are: Miss Alfrieda Sherman, Committee on Membership; James Caffee, M.D., Committee on Camps.

The LOS ANGELES DIABETES ASSOCIATION in March elected Paul O. Greeley, M.D., President; Samuel Soskin, M.D., Vice-President; Lorenz M. Waller, M.D., Secretary-Treasurer. Committee Chairmen: Roy S. Perkins, M.D., Committee on Detection and Education; William H. Grishaw, M.D., Committee on Camps. Clinical Society officers for 1954 are: Paul O. Greenley, M.D., President; Samuel Soskin, M.D., Vice-President; Lorenz M. Waller, M.D., Secretary-Treasurer.

The NEW ENGLAND DIABETES ASSOCIATION named these officers in May: Reed Harwood, M.D., President; Harry Blotner, M.D., Vice-President; C. Cabell Bailey, M.D., Secretary; L. Tillman McDaniel, M.D., Treasurer. The following Committee Chairmen were appointed: Harry Blotner, M.D., Committee on Detection; Alexander Marble, M.D., Committee on Finance.

The NEW YORK DIABETES ASSOCIATION elected the following Clinical Society officers in May: Frederick W. Williams, M.D., Chairman; Murray M. Levites, M.D., 1st Vice-Chairman; George E. Anderson, M.D., 2nd Vice-Chairman; Harold Brandaleone, M.D., Secretary-Treasurer.

The Clinical Society of this Association will present "Vascular Disease in Diabetes Mellitus," its Second Annual Symposium Day on Diabetes Mellitus, October 14 in the Auditorium, Memorial Center for Cancer and Allied Diseases, 410 East 68th Street, New York. Irving Graef, M.D., is presiding at the morning session, while the welcome will be given by Frederick W. Williams, M.D., retiring Chairman of the Clinical Society.

Papers to be delivered include "Atherosclerotic Lesions in Diabetes," by Margaret Bevans, M.D.; "Discussion," by Aaron Kellner, M.D.; "The Morphogeny of the Capillary Vascular Lesions of Diabetes," by James Berkman, M.D.; "Discussion," by Irving Graef, M.D.; "Normal Serum Lipid Metabolism," by Forrest E. Kendall, Ph.D.; "Metabolism of the Serum Lipids in Diabetes and in Arteriosclerosis," by George V. Mann, M.D.; "Discussion of Previous Two Papers," by Thomas H. McGavack, M.D., C. F. Wilkinson, M.D., and David Barr, M.D.

Robert S. Goodhart, M.D., will preside for the afternoon session, when these papers will be given: "The Capillary Vascular Lesion—Its Clinical Manifestations and Significance," by Louis Leiter, M.D.; "Discussion,"

Henry Dolger, M.D.; "Present Day Concepts of Diabetic Retinopathy," by Isadore Givner, M.D.; "Discussion," by George Wise, M.D.; "Coronary Artery Disease in the Diabetic," by Alexander Marble, M.D.; "Discussion," by Gerald Friedman, M.D.; "Prevention of Vascular Disease in the Diabetic," by Laurance W. Kinsell, M.D.; "The Management of the Diabetic with Vascular Disease," by H. B. Mulholland, M.D.; "Discussion," by Edward Tolstoi, M.D., Beverly Chew Smith, M.D., and Elaine P. Ralli, M.D.; "Closing Remarks," by Herbert Pollack, M.D.

At the evening reception and dinner program to be held at the New York Academy of Sciences, Murray M. Levites, Chairman of the Clinical Society, will preside. Ancel Keys, Ph.D., will speak on "Relative Obesity and the Blood Chemistry in Man."

The NORTH DAKOTA DIABETES ASSOCIATION chose these officers in May: P. Roy Gregware, M.D., President; Donald Barnard, M.D., Vice-President; Martin Hochhauser, M.D., Secretary. E. A. Haunz, M.D., is Chairman of the Committee on Detection and Education.

The PITTSBURGH DIABETES ASSOCIATION elected Clinical Society officers in May: Thomas McC. Mabon, President; Meyer Bloom, M.D., 1st Vice-President; Donald Y. Cameron, M.D., 2nd Vice-President; L. Lewis Pennock, M.D., Secretary-Treasurer.

The ROCHESTER REGIONAL DIABETES ASSOCIATION (New York) elected the following officers for 1954: John R. Williams, Jr., M.D., President; Joseph L. Izzo, M.D., Vice-President; E. B. Millard, Jr., M.D., Secretary.

The ST. LOUIS DIABETES ASSOCIATION elected these officers in June: Mrs. C. Paul Tiley, President; Henry E. Oppenheimer, M.D., 1st Vice-President; Mr. Samuel B. Edison, 2nd Vice-President; William H. Olmsted, M.D., Secretary; Mr. Jack R. Cutter, Treasurer.

The TENNESSEE DIABETES ASSOCIATION named new officers in April: Robert F. Ackerman, M.D., President; Addison B. Scoville, Jr., M.D., Vice-President; Jean M. Hawkes, M.D., Secretary and Chairman, Committee on Detection and Education. Albert S. Easley, M.D., continues as Chairman of the Committee on Camps.

The TEXAS DIABETES ASSOCIATION in May named George M. Jones, M.D., President; Laurence B. Reppert, M.D., 1st Vice-President; William S. Barcus, M.D., 2nd Vice-President; Hugo T. Engelhardt, M.D., Secretary-Treasurer.

The WEST CENTRAL DIABETES ASSOCIATION elected the following officers in May: Edmond M. Walsh, M.D., President; Sanford M. Rathbun, M.D., President Elect; Morris Pepper, M.D., 1st Vice-President; Robert S. Long, M.D., 2nd Vice-President; Michael Crofoot, M.D., Secretary; John D. Hartigan, M.D., Treasurer. J. A. Pleiss, M.D., Chairman, Committee on Detection and Education; John D. Hartigan, M.D., Chairman, Committee on Finance; Floyd Rogers, M.D., Chairman, Committee on Camps, were appointed. Clinical Society officers for 1954 are: Edmond M. Walsh, M.D., President; Robert S. Long, M.D., 2nd Vice-President; Michael Crofoot, M.D., Secretary; John D. Hartigan, M.D., Treasurer.

News Notes

Personals

Herbert Pollack, M.D., Consultant to the Surgeon General, Department of the Army, since 1951, has been appointed Associate Professor of Clinical Medicine at New York University-Bellevue Medical Center's Postgraduate Medical School.

Dr. Pollack was in Formosa in June, where he spoke to the Taipeh Medical Society. The subject of his talk was "Diabetes in the East and West."

DeWitt Stetten, Jr., M.D., has been appointed Associate Director in Charge of Research, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md. Dr. Stetten will plan, develop and execute an integrated laboratory and clinical research program.

At the time of his appointment to the National Institutes of Health, Dr. Stetten was a member of the Public Health Research Institute of the City of New York, Inc., where he was Chief of the Division of Nutrition and Physiology.

Priscilla White, M.D., Boston, was awarded the honorary degree of Doctor of Science from Middlebury College June 13, for her work with diabetic women and children.